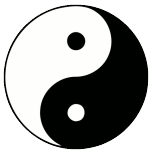


resting state: issues and opportunities

Catie Chang

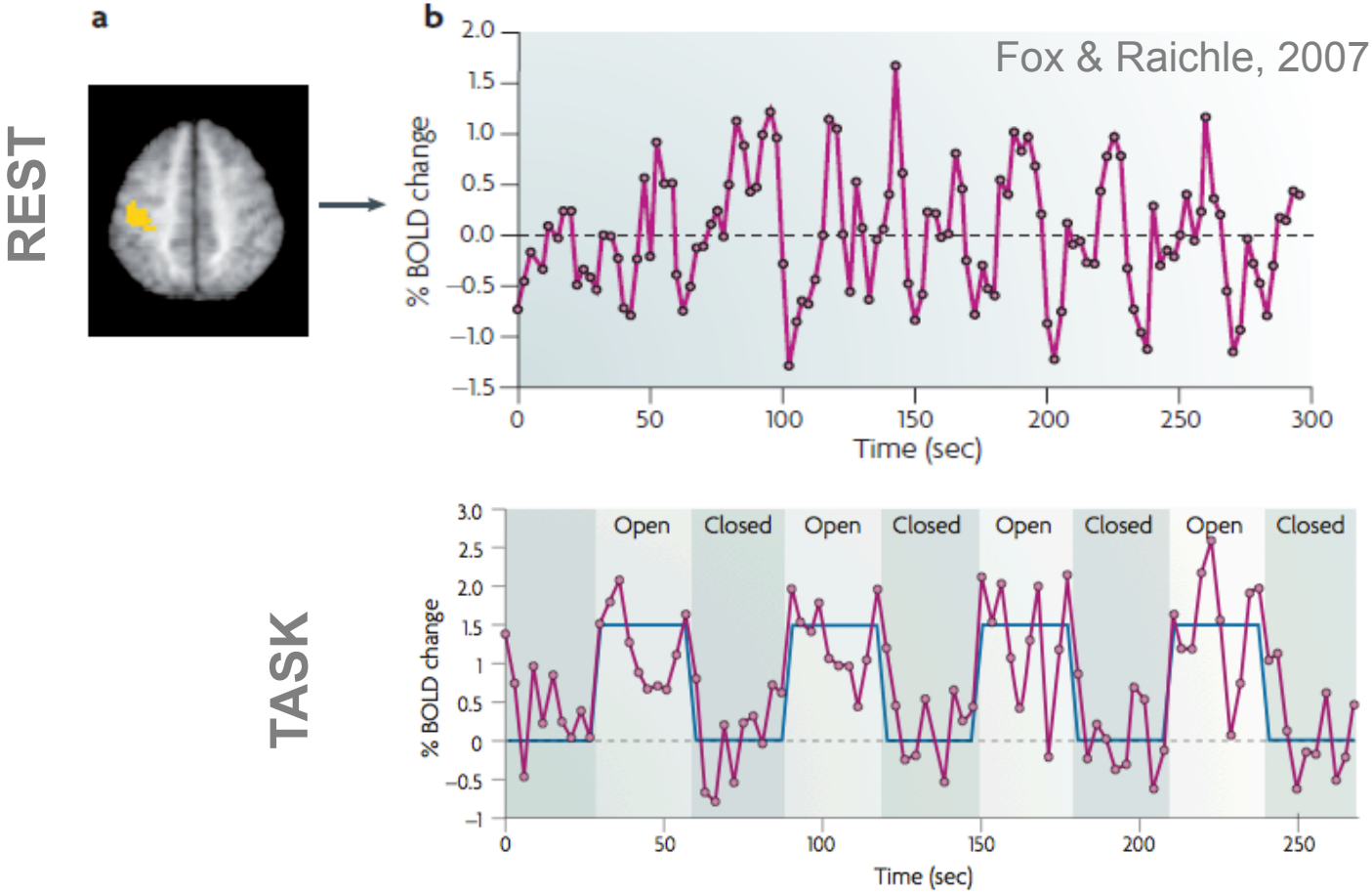
Section on Advanced MRI, NINDS, NIH

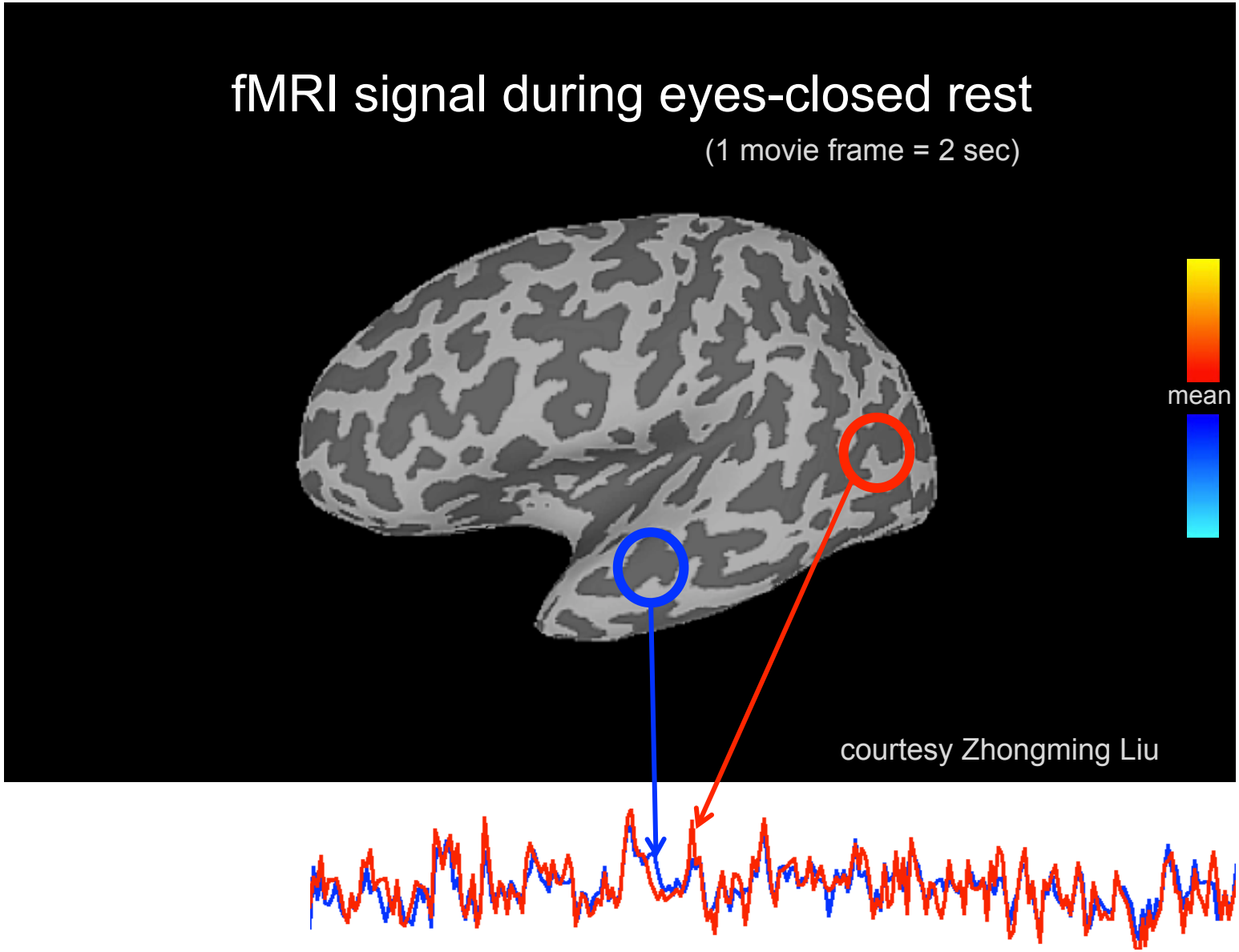
catie.chang@nih.gov

Advanced MRI

Resting-state fMRI

- no task / stimuli
- minimal instructions (“close your eyes, stay awake...”)

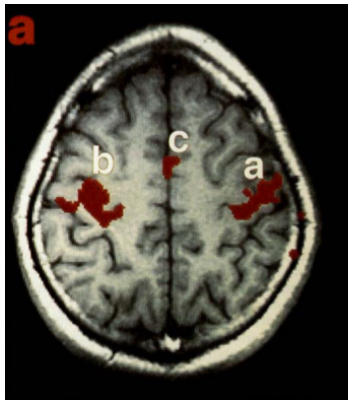




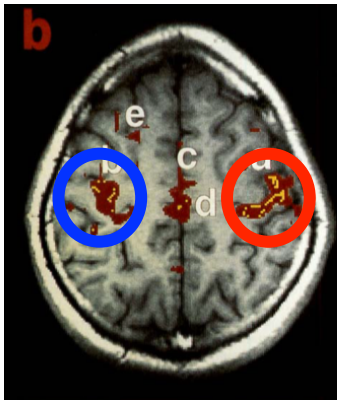
relationship between time series: “functional connectivity”

Introducing resting-state fMRI ...

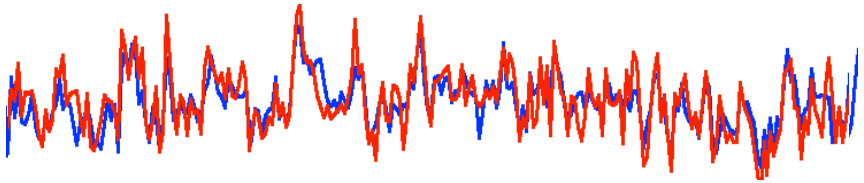
- Bharat Biswal et al., 1995



Finger-tapping activation



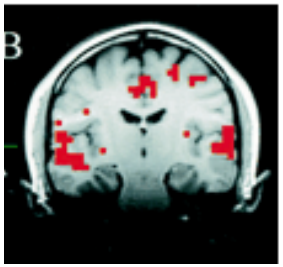
Correlation during resting-state scan



time series during resting-state scan

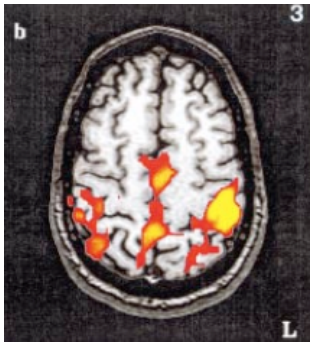
Resting-state functional connectivity

Auditory

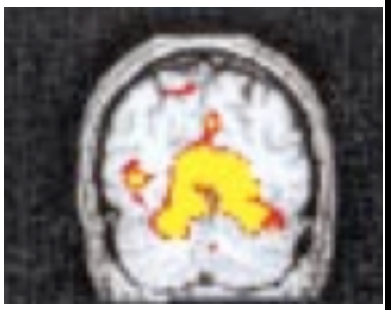


Cordes et al. 2000

Sensorimotor

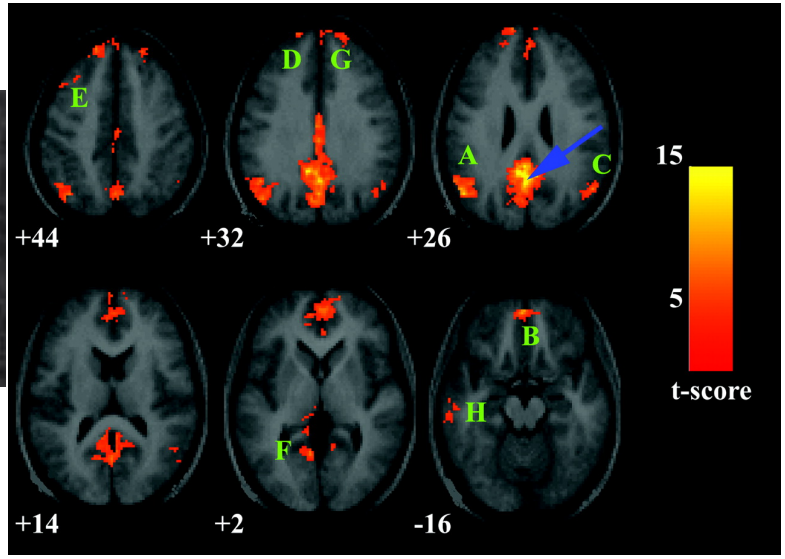


Visual

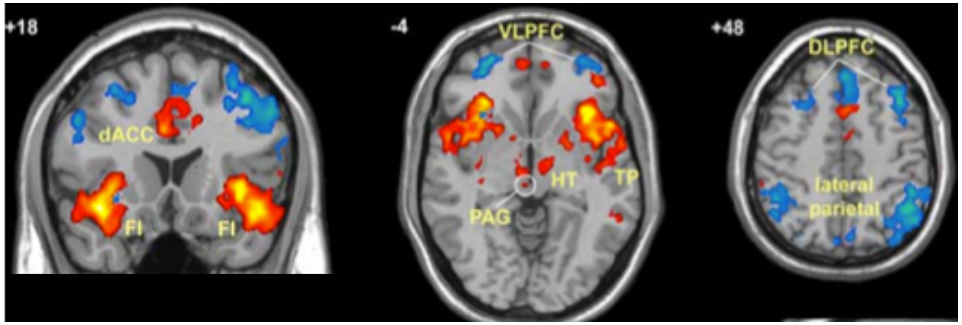


Lowe et al. 1998

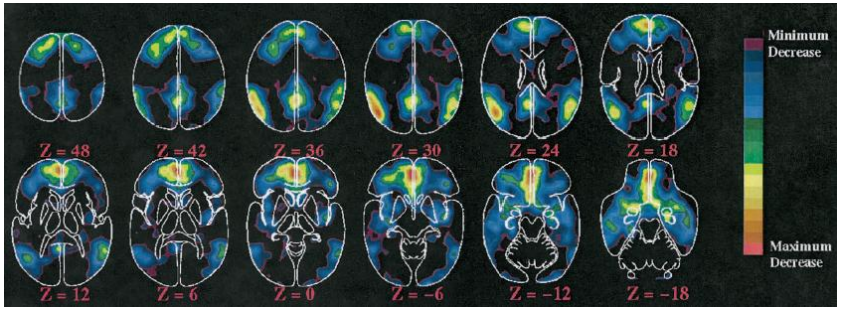
Default Mode Network



Greicius et al. 2003



Seeley et al. 2007

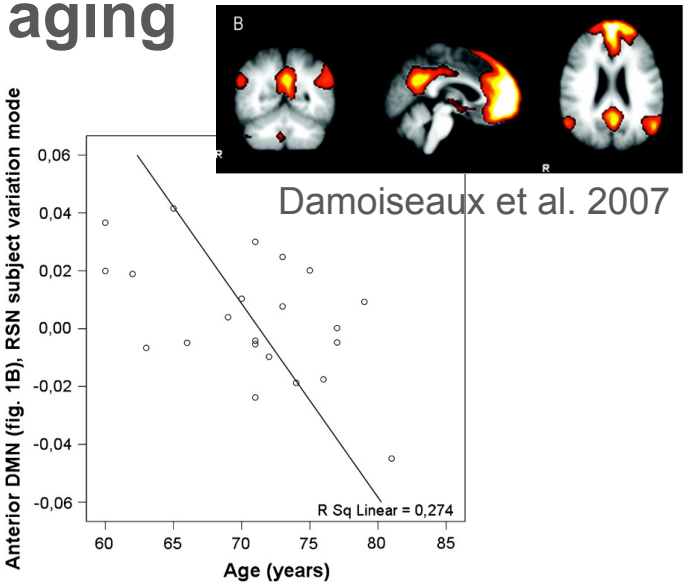


Raichle et al. 2001

Task-free mapping of functional networks!

Applications

aging

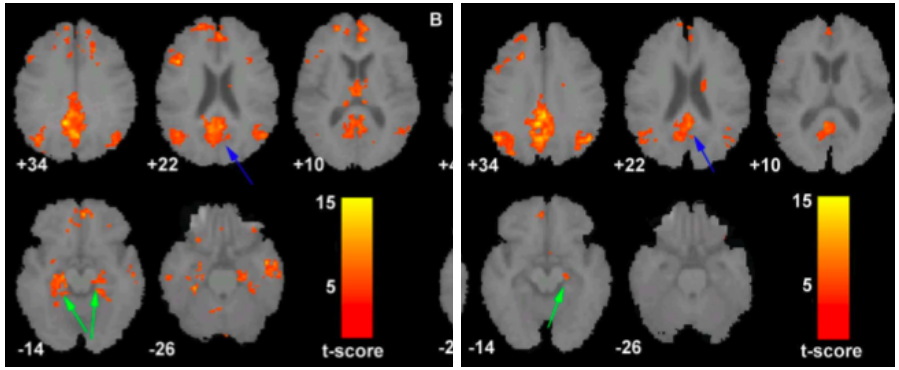


Damoiseaux et al. 2007

Alzheimer's

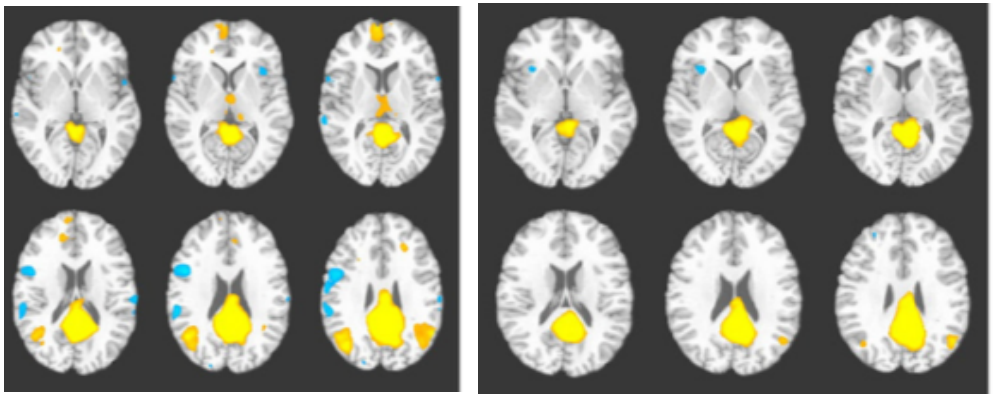
Healthy control

Alzheimer's



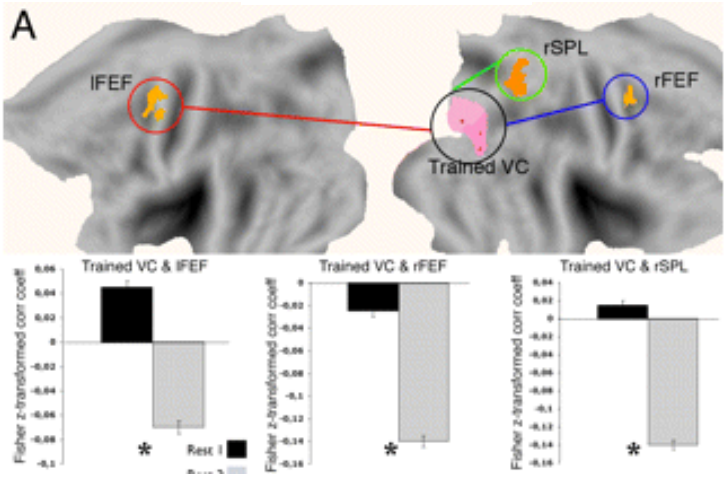
Greicius et al. 2004

sleep



Horovitz et al, 2009

learning



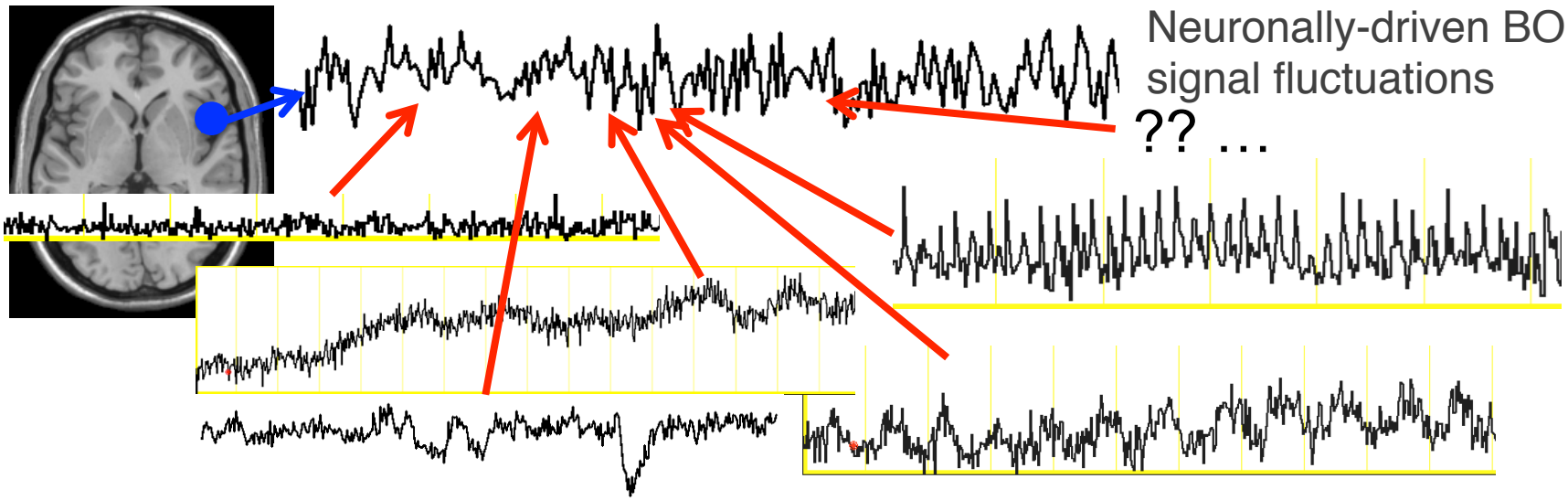
Lewis et al, 2009

Issues
& Opportunities

- Noise
- Signal origin
- Resting states

Noise

Noise in fMRI

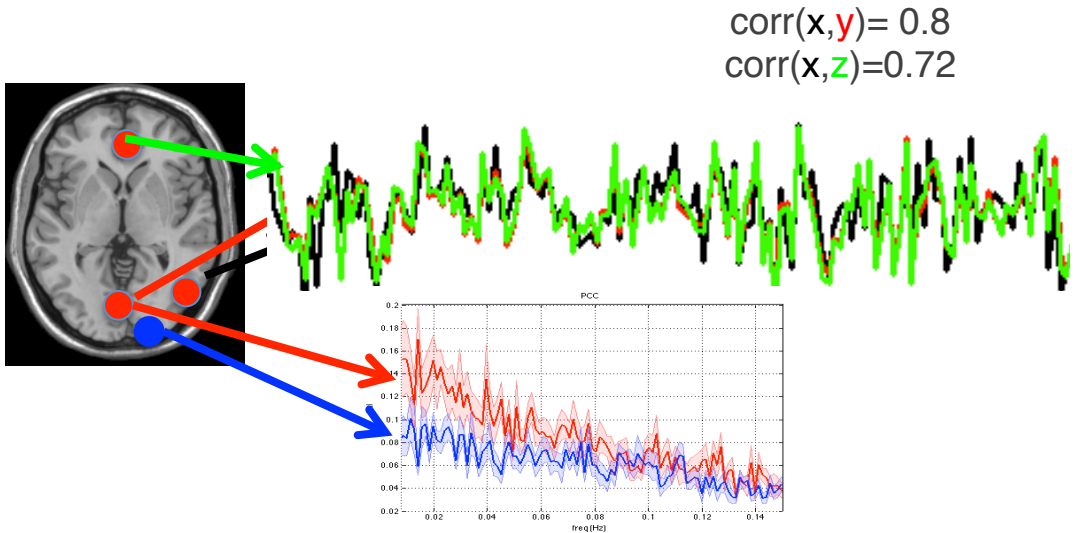


- Thermal noise
- Slow drifts (magnet instability; e.g. gradient heating)
- Head motion
- **Physiological processes (respiration, cardiac..)**

Importance of noise reduction for resting-state fMRI

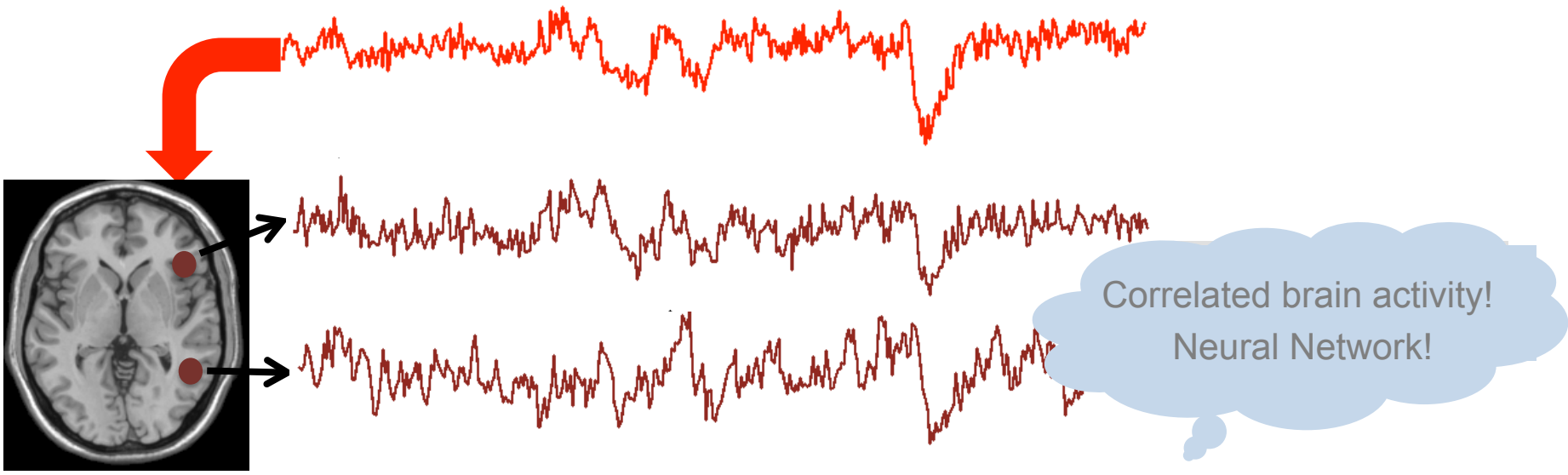
- Harder to separate signal v. noise (cf. task-based)
  - no model
  - no event-locked averaging

- Operating directly on the noisy time series themselves



Meunier et al. 2010

Impact of noise on correlations



- Noise can:
  - inflate correlations (false positives; Type I)
  - bury true correlations (false negatives; Type II)

Noise in resting-state fMRI

- Effects are complex, ill-understood
- Noise reduction methods exist, but....

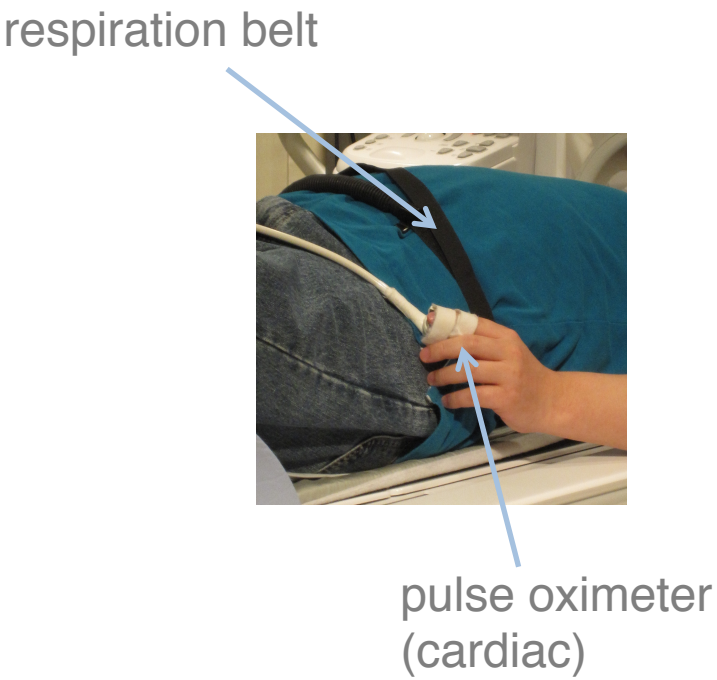
  ....no universally accepted “correction” pipeline
- Desire principled methods for correction

→ **understand noise sources**

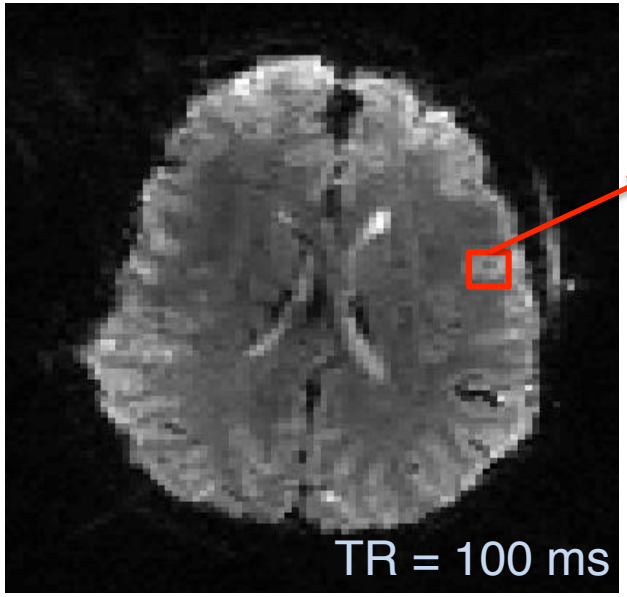
+ tradeoffs of correction methods

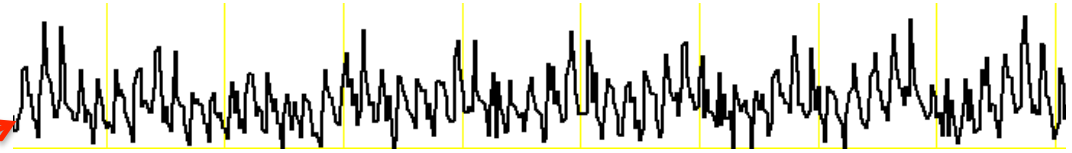
Outline

- Physiological noise
  - Noise sources
  - Measurement-based noise reduction
- Data-driven
  - global signal regression
  - non-gray-matter regression
  - ICA
  - band-pass filtering



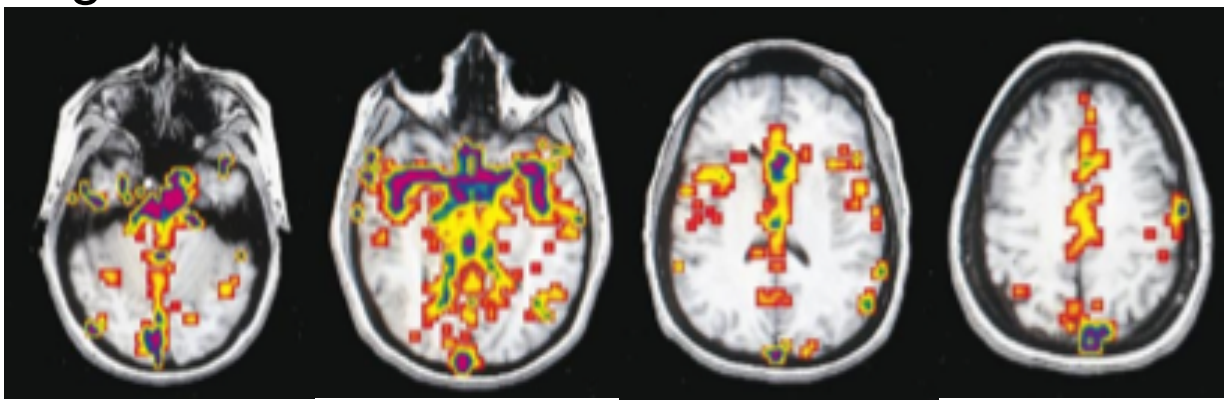
Cyclic cardiac noise





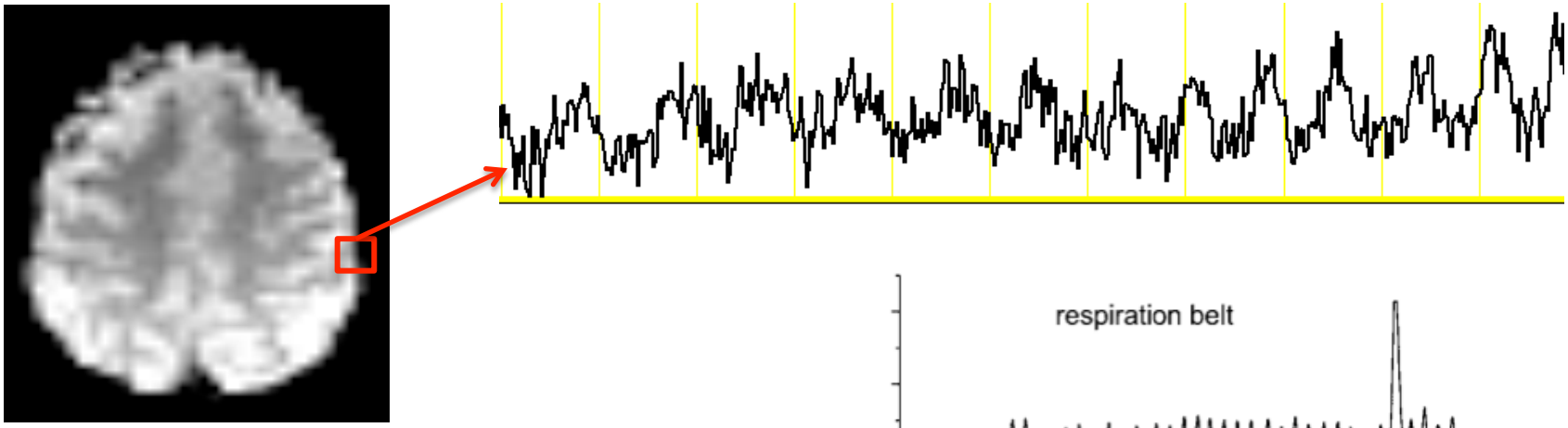
- pulsatile motion of vasculature
  - T_1 inflow (unsaturated blood)

- Mainly affects areas within / bordering CSF & large vessels

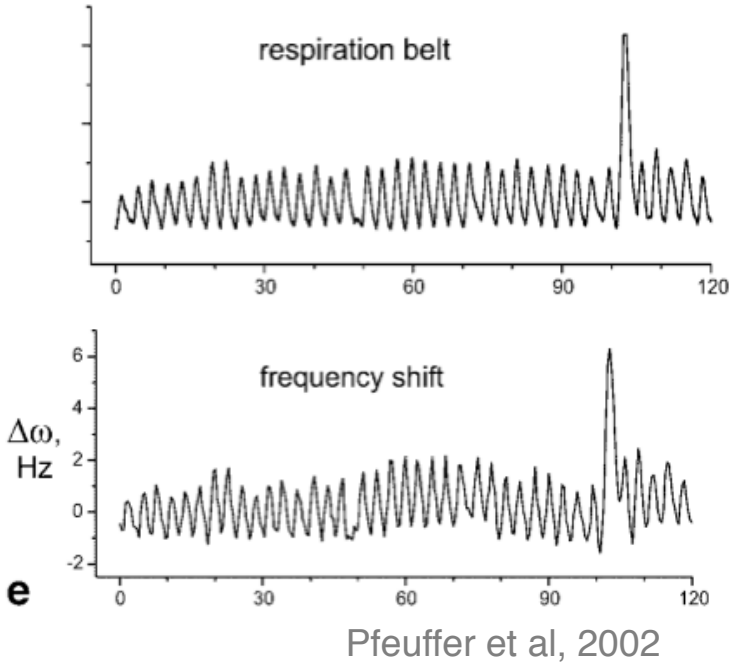


- Dagli et al, 1999

Cyclic respiration noise

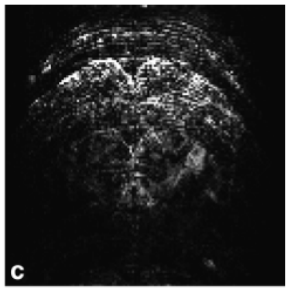


- Motion of abdomen during breathing causes shifts in B_0 (dynamic off-resonance)
  - spatial shift (EPI) or blur (spiral)

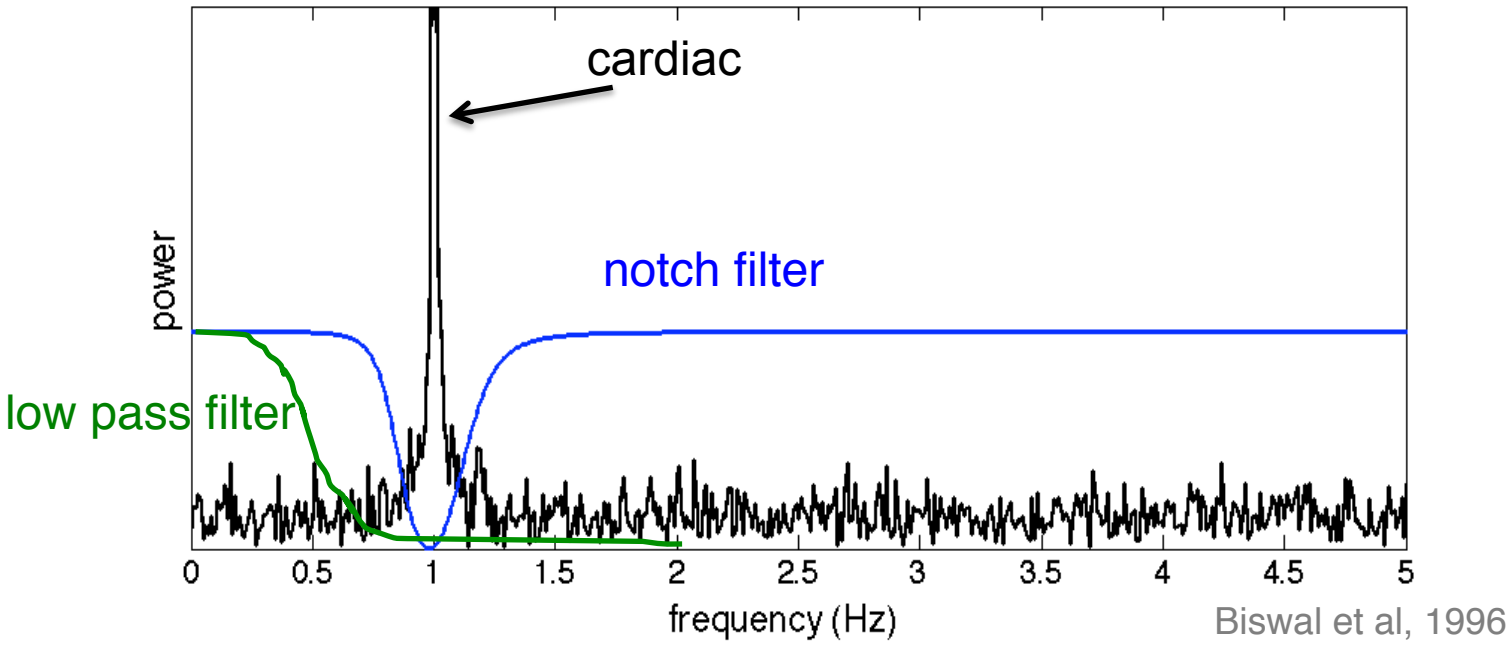


Pfeuffer et al, 2002

- Global; most visible in areas around edges of brain / tissue compartments



Filtering cyclic noise?

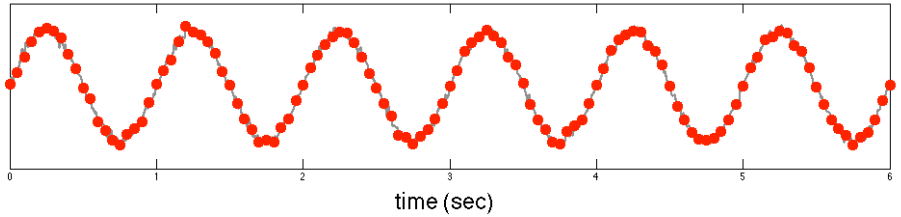


Biswal et al, 1996

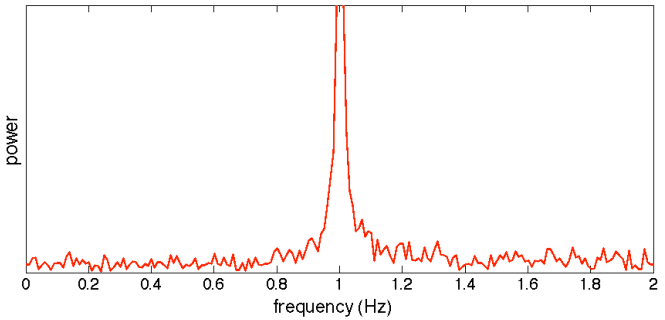
✧ Only works if TR is fast enough to avoid aliasing (which is rarely the case)

Aliasing

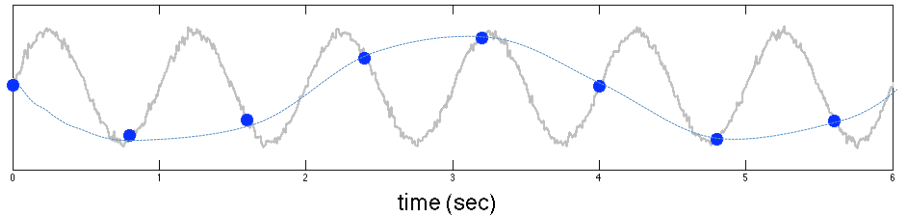
TR = 50 ms



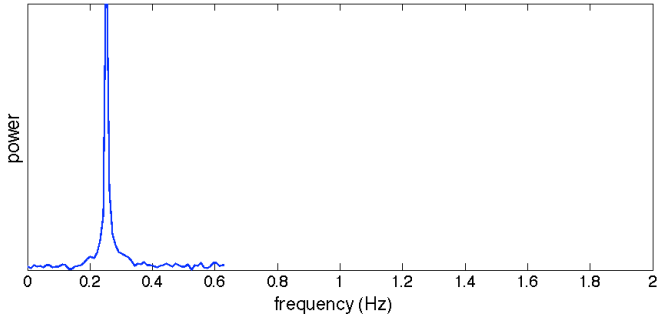
Fourier transform



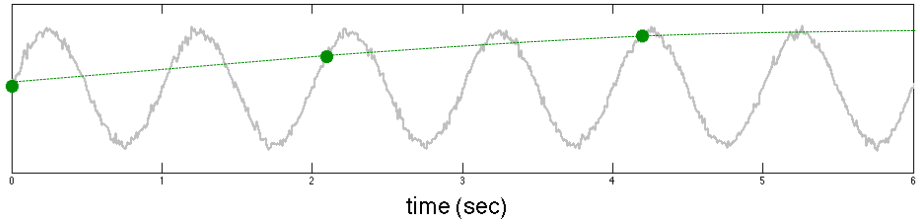
TR = 800 ms



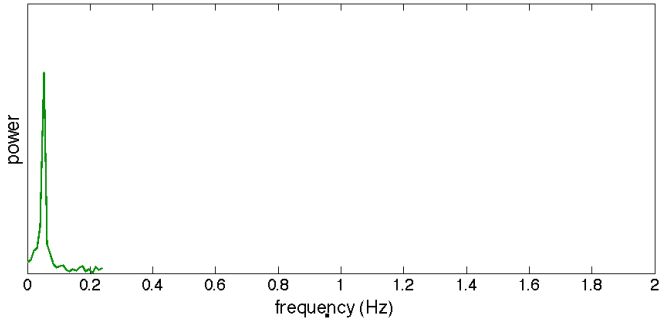
Fourier transform



TR = 2.1 s

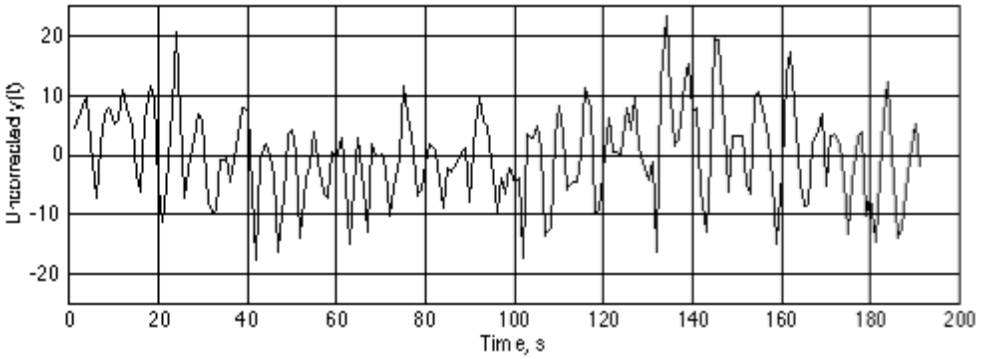


Fourier transform

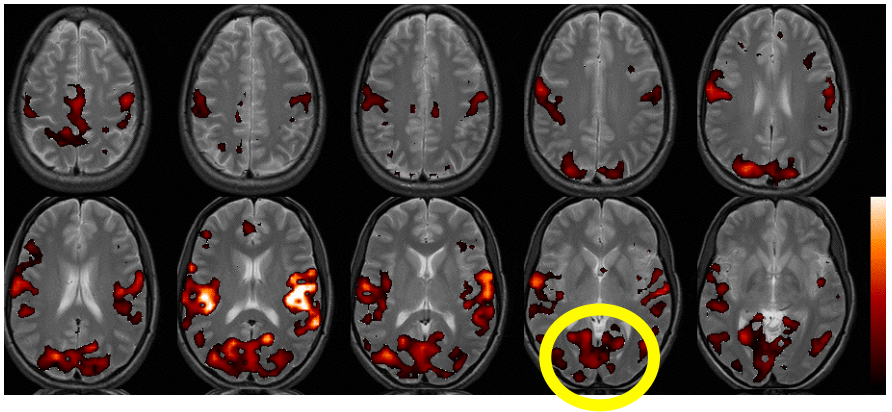


RETROICOR

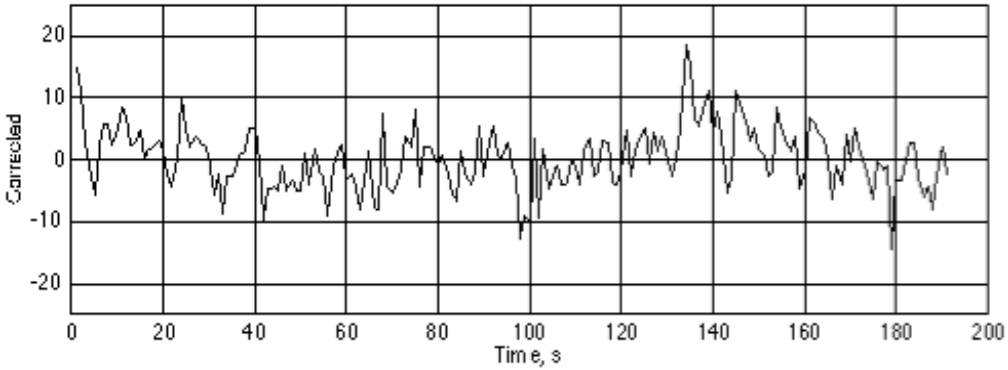
before retroicor



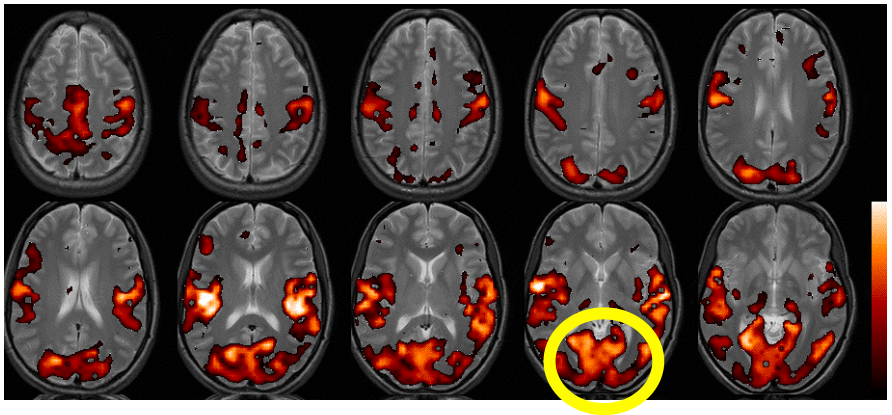
before retroicor



after retroicor



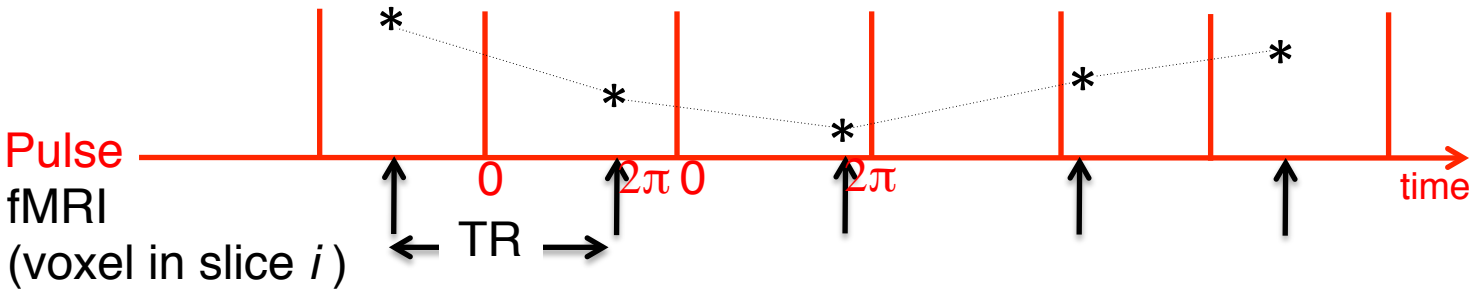
after retroicor

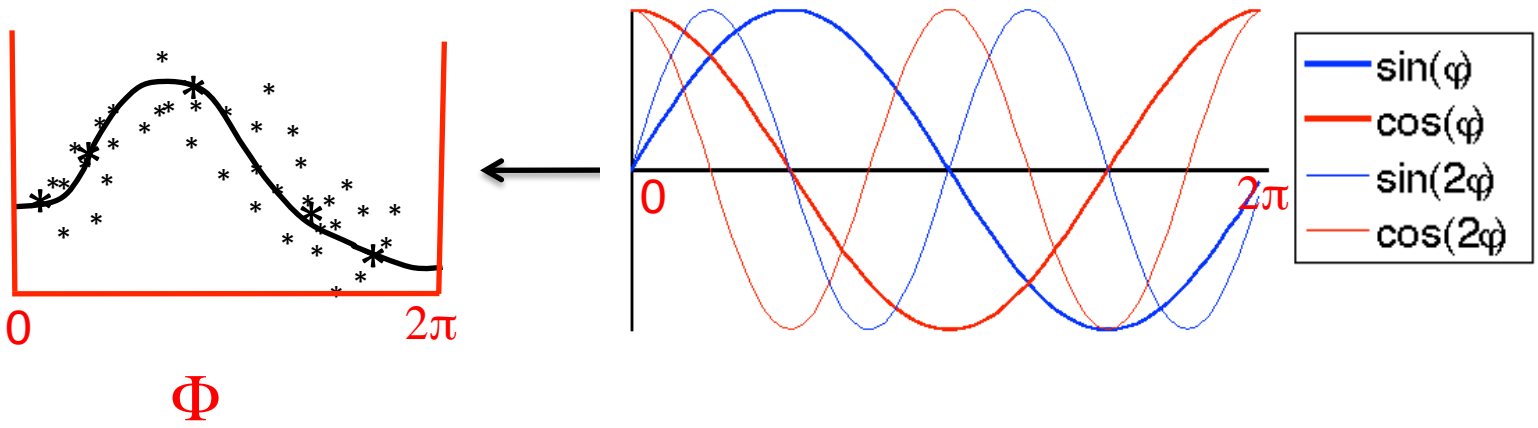


TR = 1 sec

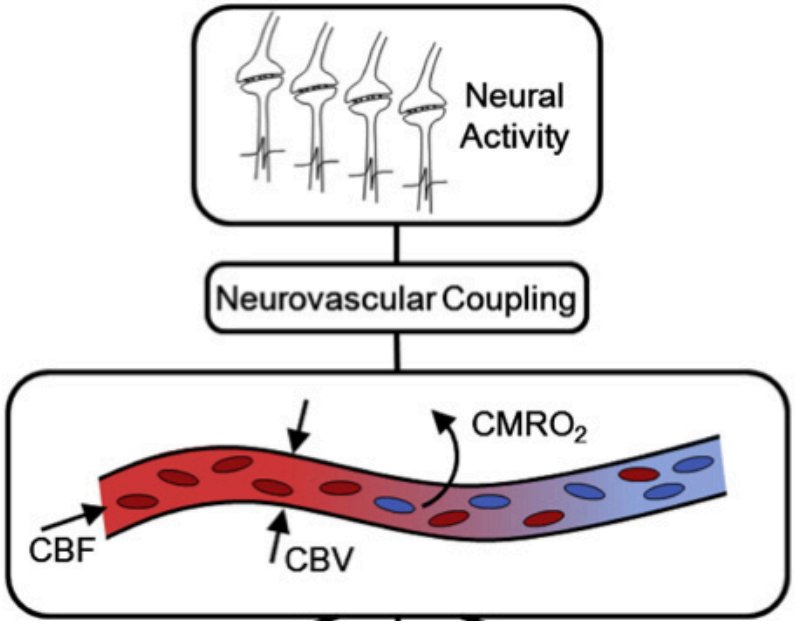
Glover et al, 2000

RETROICOR (Glover et al. 2000)





“BOLD” physiological noise

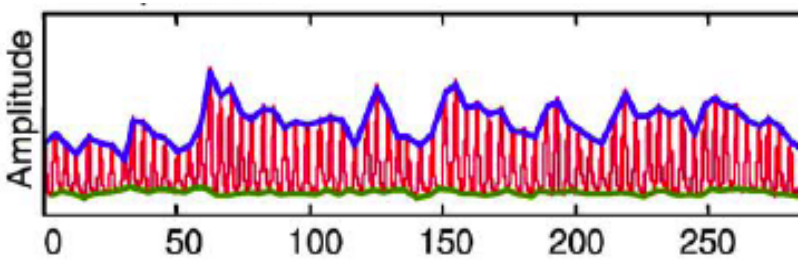


Murphy et al., 2013

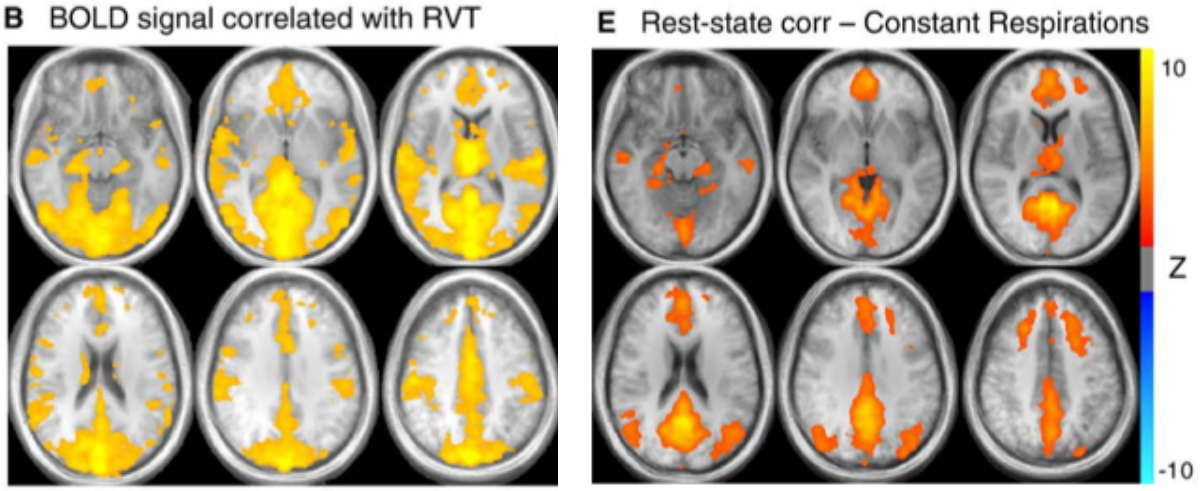
- BOLD is a function of $CMRO_2$, CBF, CBV
- Breathing and cardiac actiity also alter CBF and CBV independently of changes in neural activity
  - non-neuronal BOLD signal change!
  - slow (hemodynamic), T2* contrast, affects gray matter

BOLD physiological noise: respiratory variations

- variations in breathing depth and rate
  - alters [CO_2]
    - → vasodilation
      - → alters CBF, CBV
  - affects gray matter

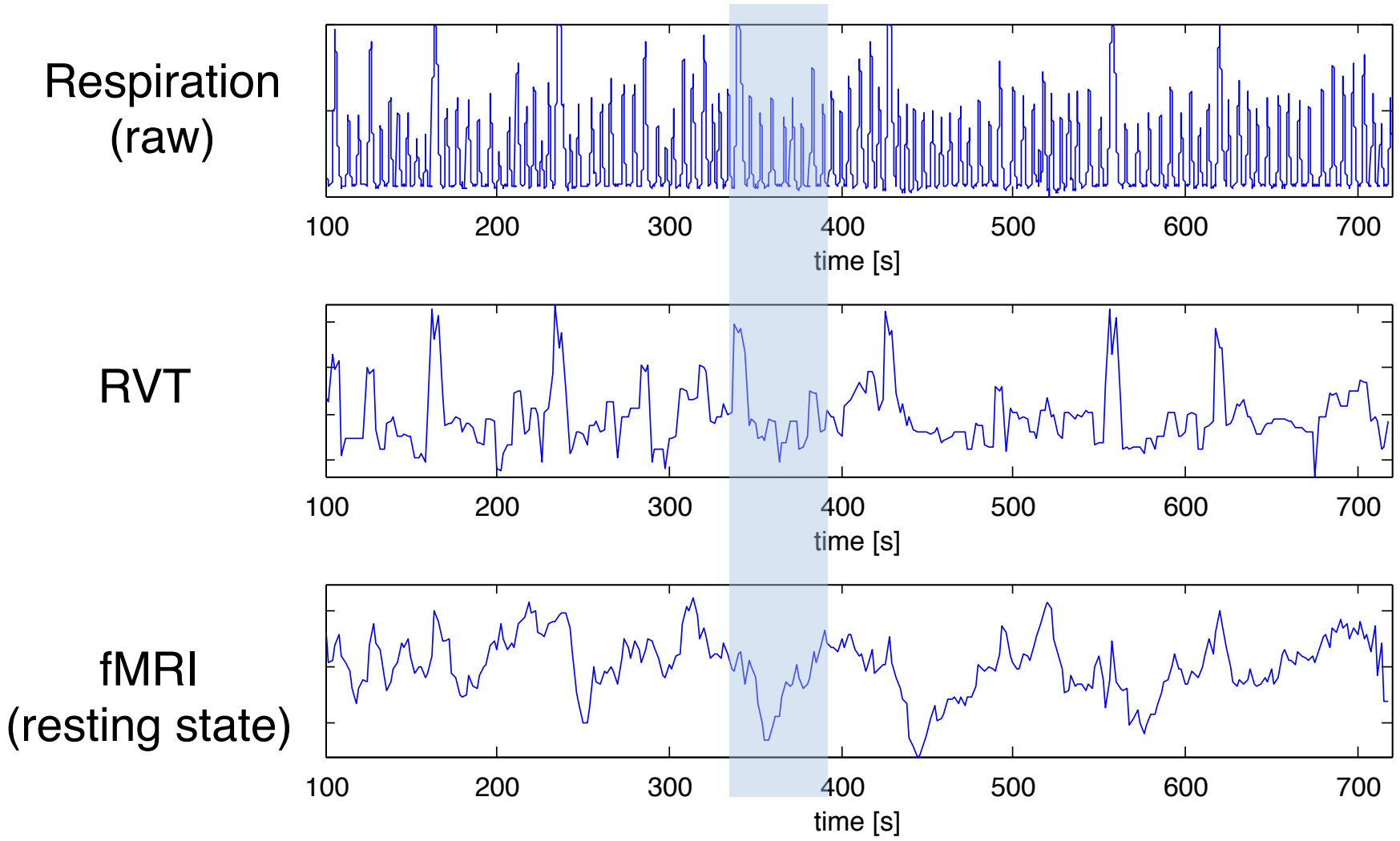


Birn et al., 2006



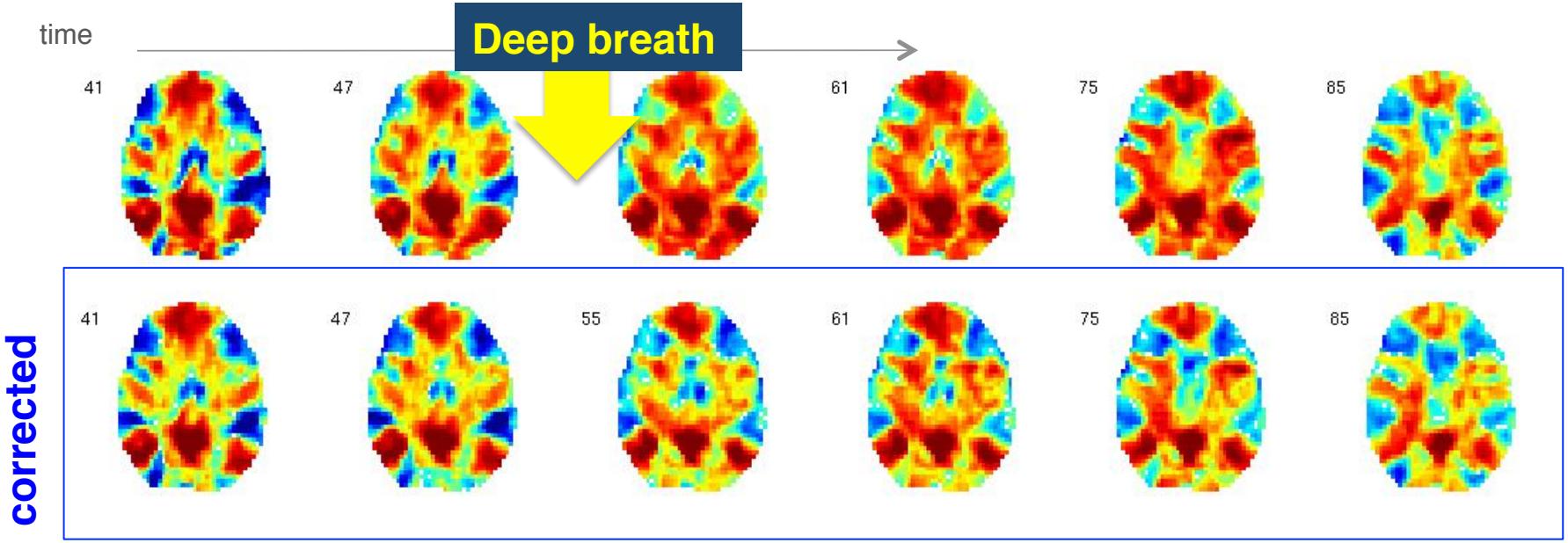
Birn et al., 2006

Correcting for respiratory variations

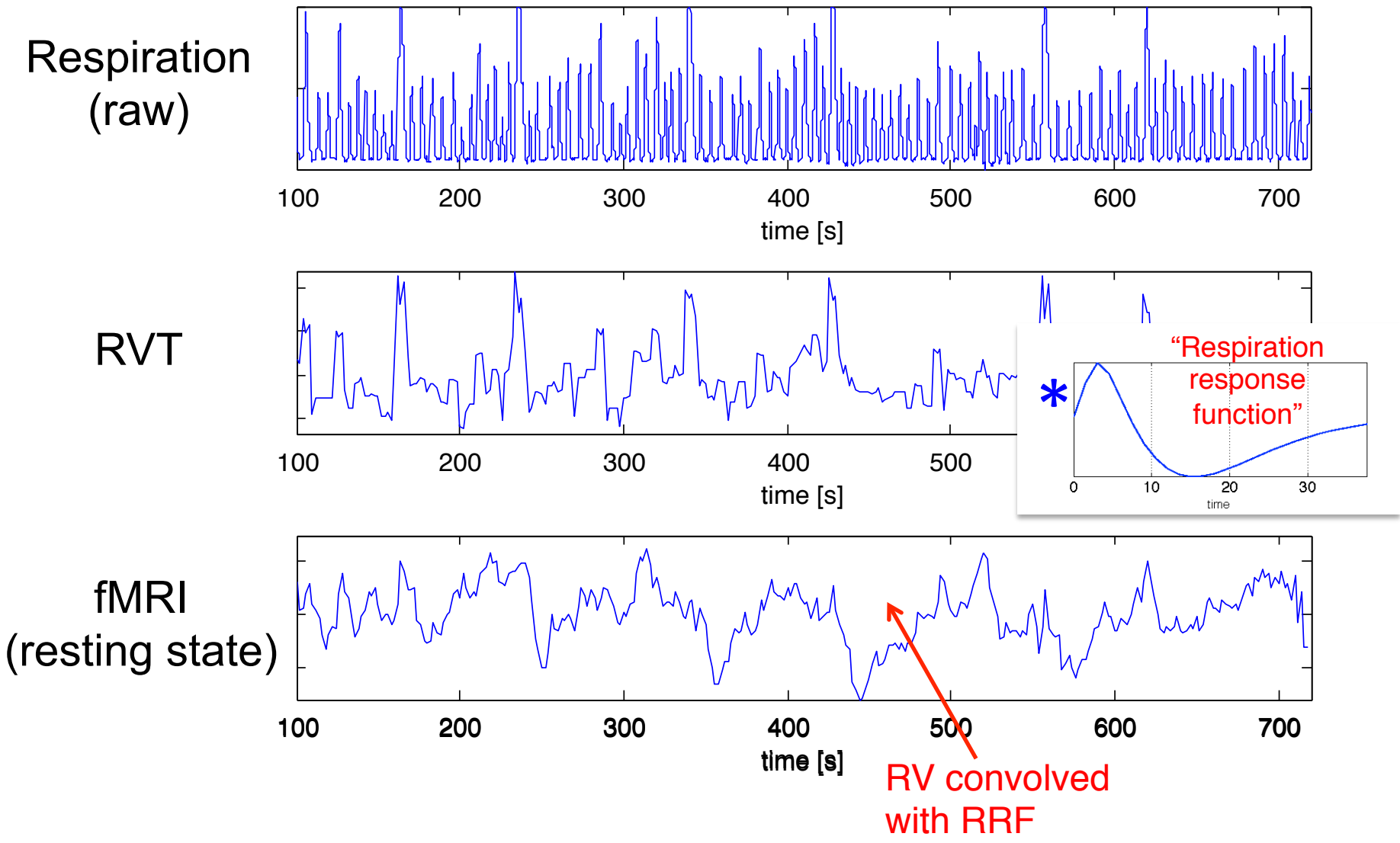


Deep breaths can inflate resting-state correlations

Seed-based correlation with PCC in successive 1-min intervals



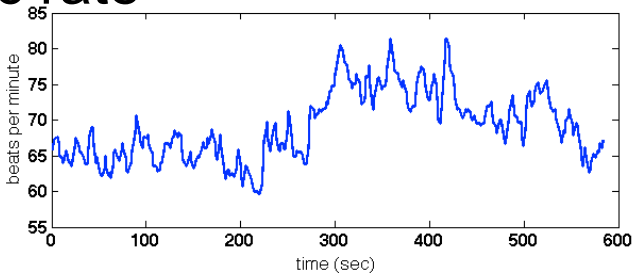
Correcting for respiratory variations



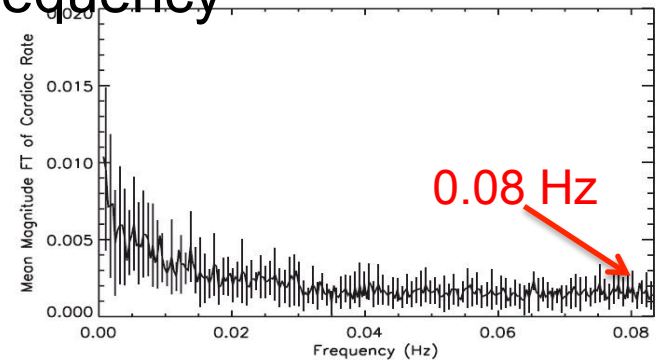
Birn et al., 2008; Chang et al., 2009

Cardiac rate variations

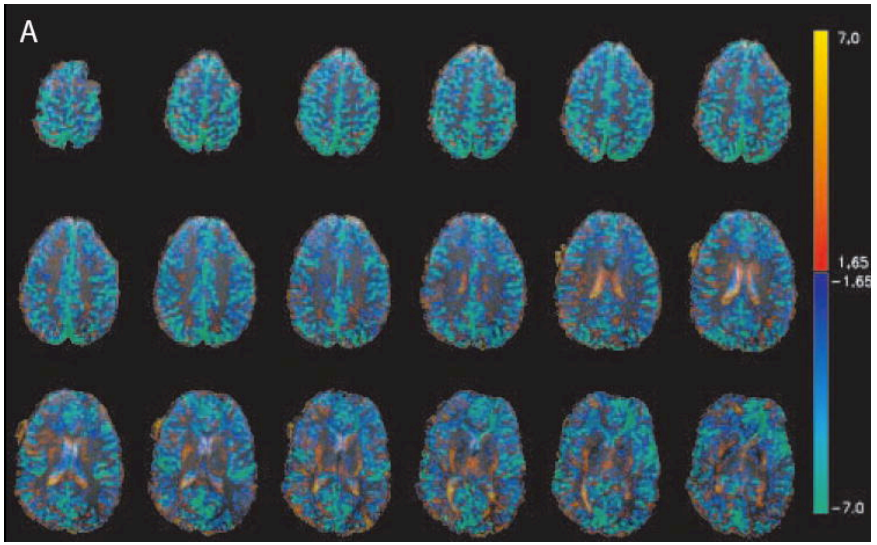
Cardiac rate



Low frequency



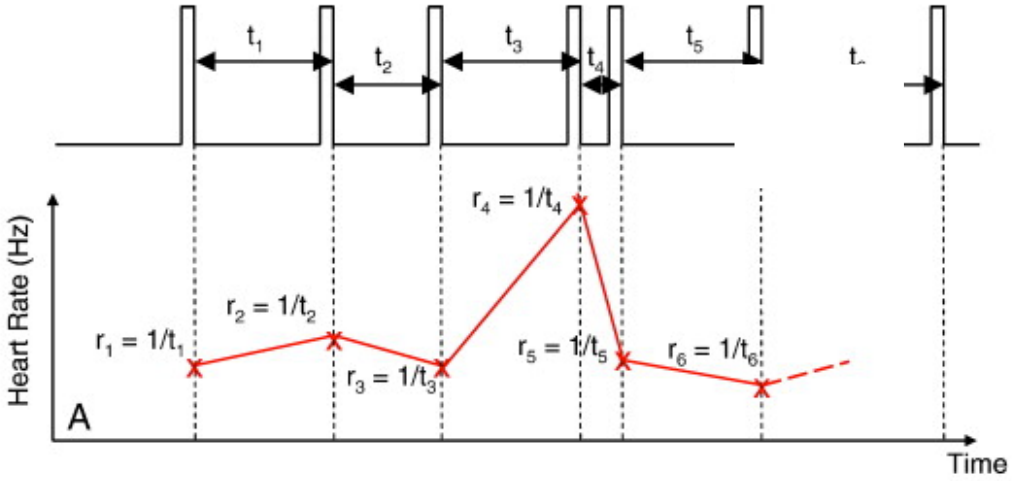
Widespread correlations with gray matter



Shmueli et al., 2007

Correcting for cardiac rate variations

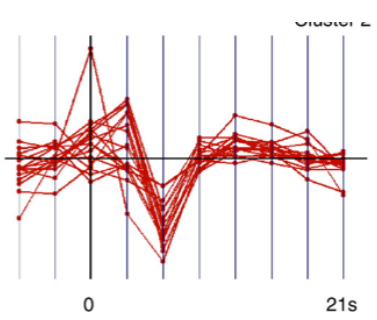
- Convert heart beats (R waves) into HR time series



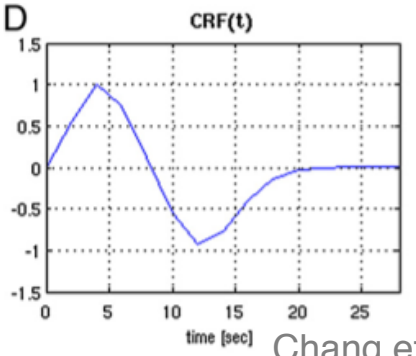
Shmueli et al, 2007

- beat-to-beat
- sliding window
- point process
- ..

- Regress shifted copies - or -
- Convolve with “cardiac response function” to obtain one nuisance regressor



deMunck et al, 2008

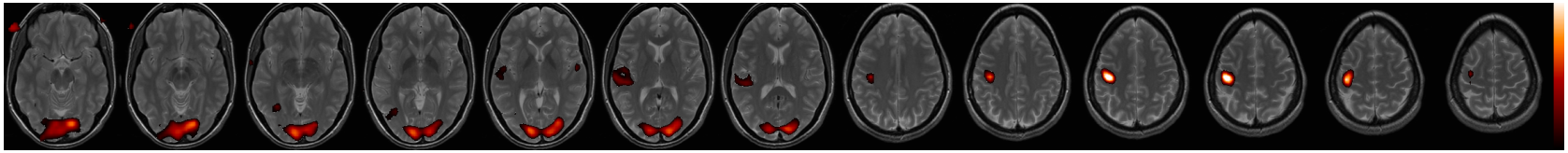


Chang et al, 2009

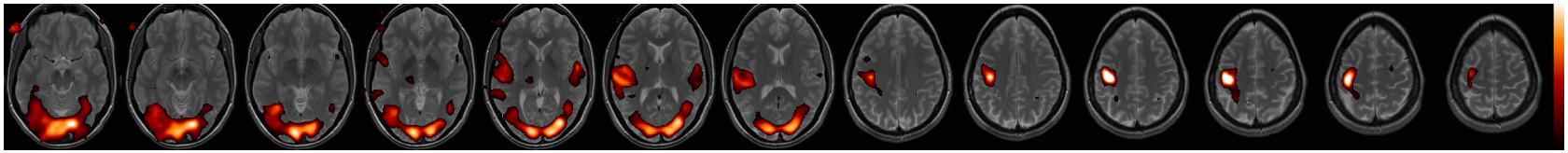
Impact of ‘BOLD’physiological noise correction

- on task activation:

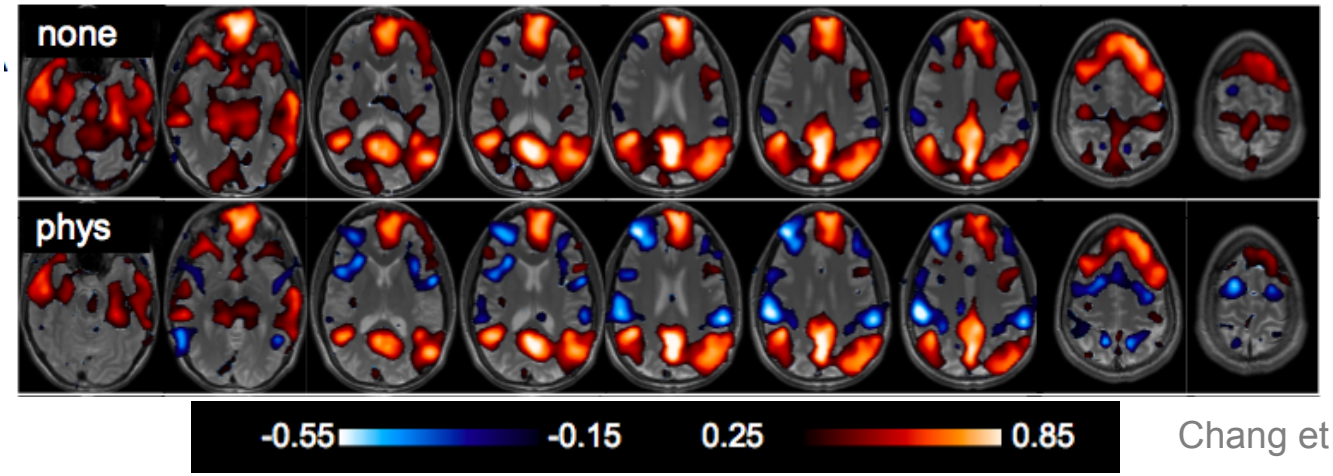
RETROICOR only



RETROICOR & RVHRcor



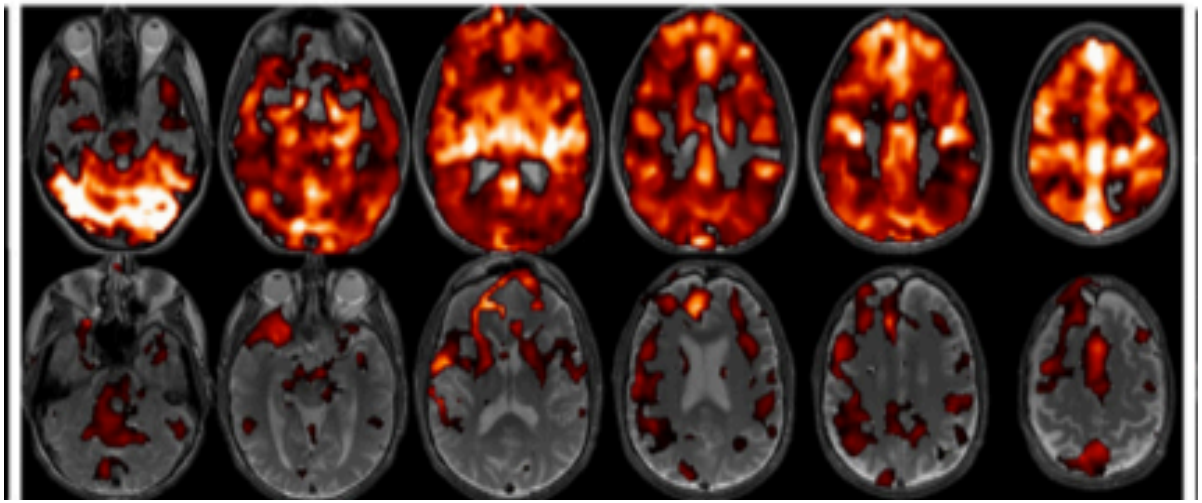
Impact of ‘BOLD’ physiological noise correction



Chang et al., 2009

subject 1

subject 2

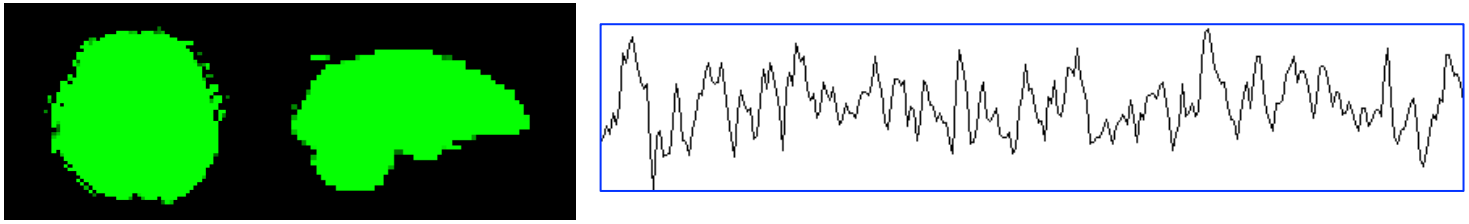


Outline

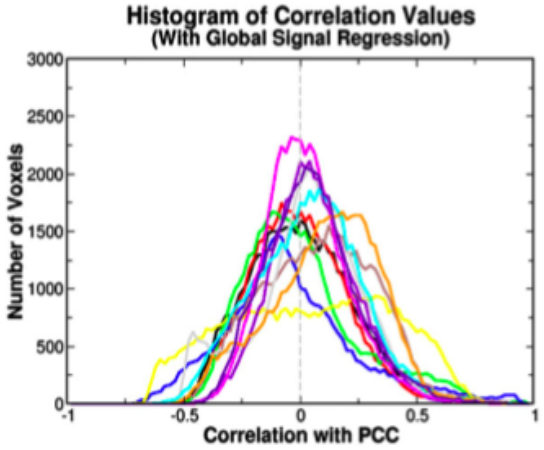
- Physiological noise
  - Noise sources
  - Measurement-based noise reduction
- Data-driven
  - global signal regression
  - non-gray-matter regression
  - ICA
  - band-pass filtering

Global signal regression

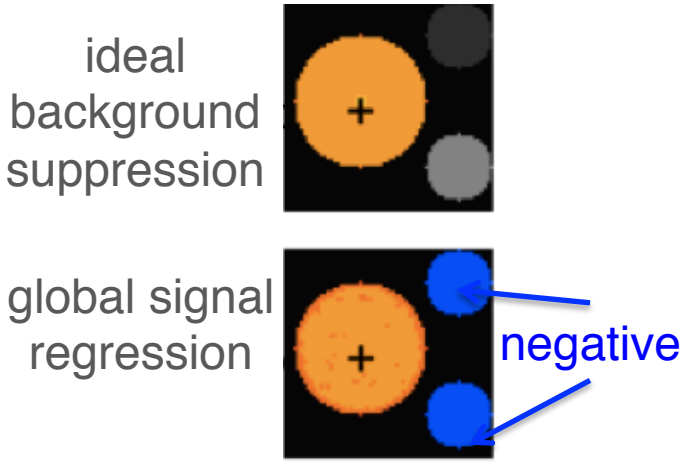
- Calculate the whole-brain average signal and include as a nuisance regressor



- Some part of the global signal may be neural
- Mathematically enforces centering of pairwise correlation distribution (creates negative correls)



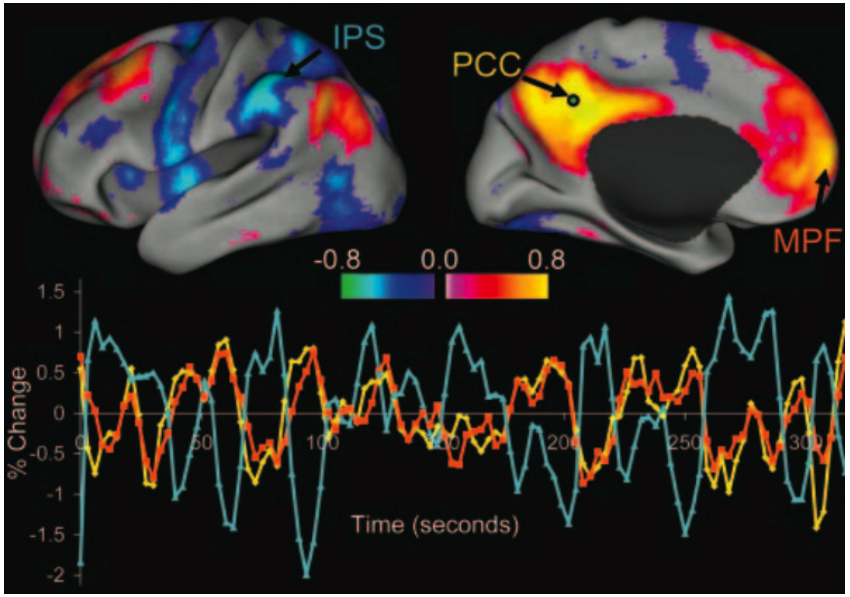
Murphy et al, 2009



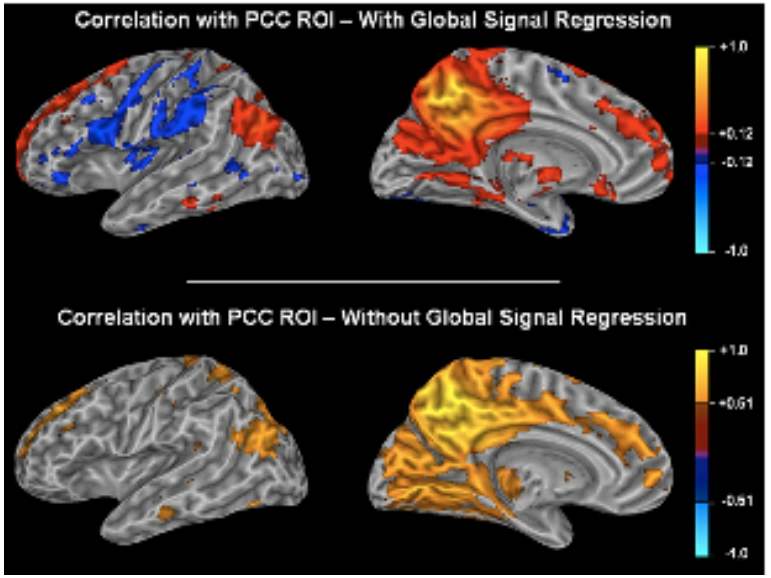
Saad et al, 2012

Global signal removal: issues

- anti-correlated resting state networks...?



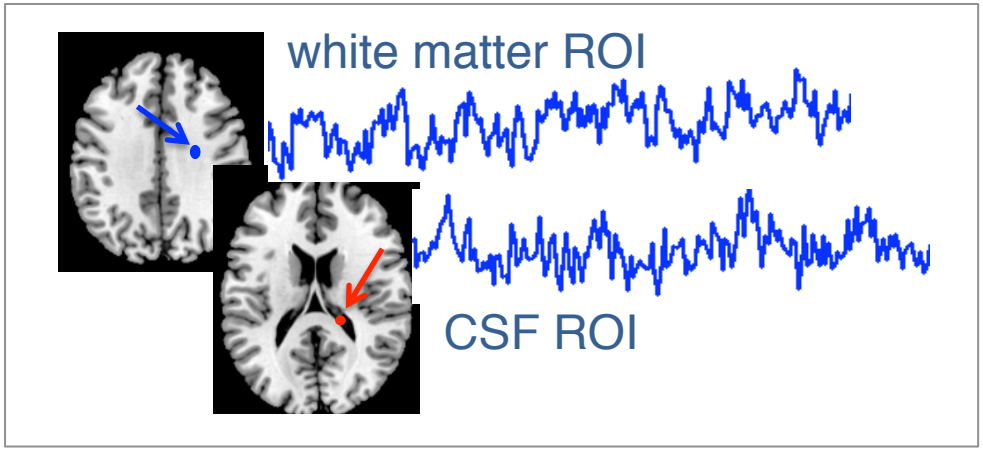
Fransson 2005, Fox et al, 2005



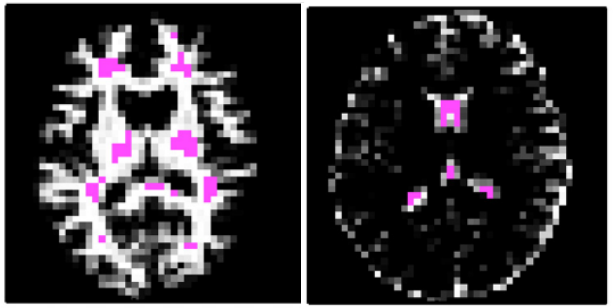
Murphy et al, 2009

Non-gray-matter nuisance regressors

- Use signals from white matter, CSF, large vessels, etc. as nuisance regressors
  - assumption: these regions carry no signals of interest, but perhaps some common noise



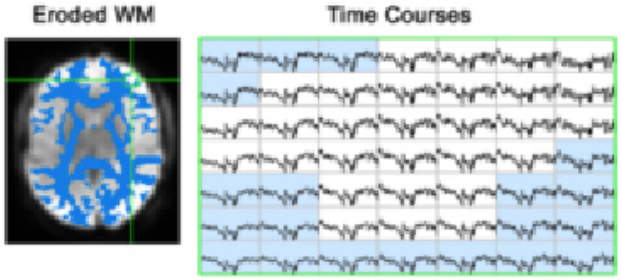
"CompCor": Behzadi et al., 2007



Temporal principal component analysis

Extract top N components as nuisance regressors

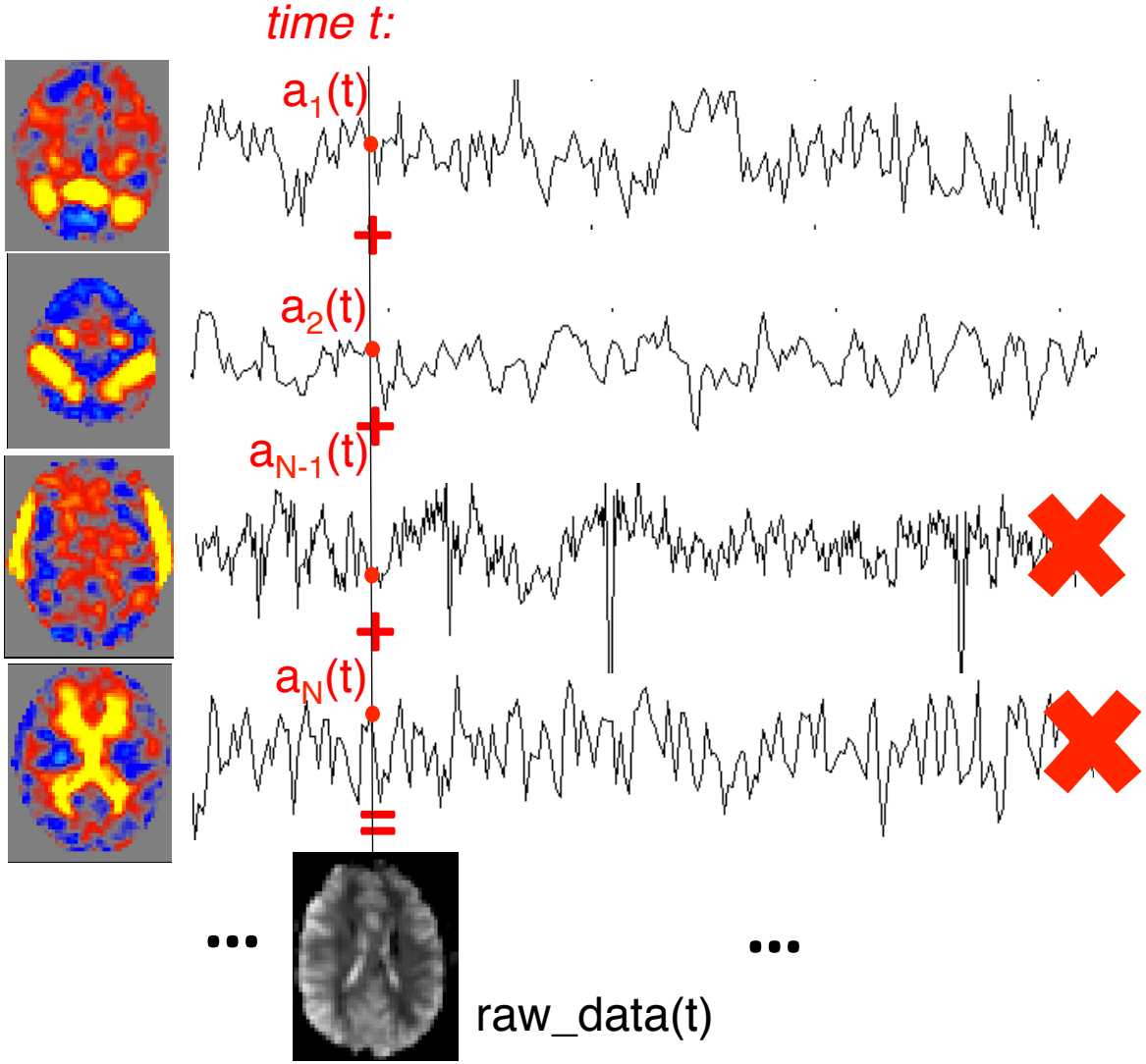
ANATICOR: Jo et al., 2010



Use WM within a neighborhood around each gray matter voxel

Spatial ICA

- Decompose 4D (volume x time) fMRI dataset into mixture of fixed spatial components with time-dependent weights

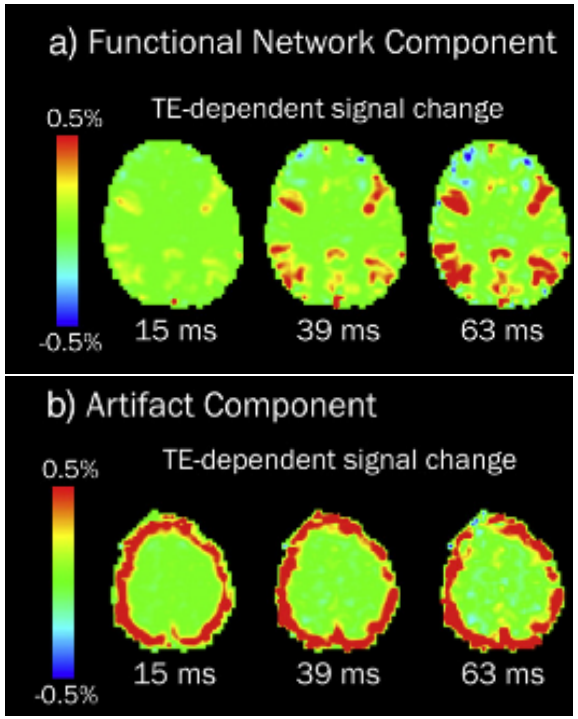


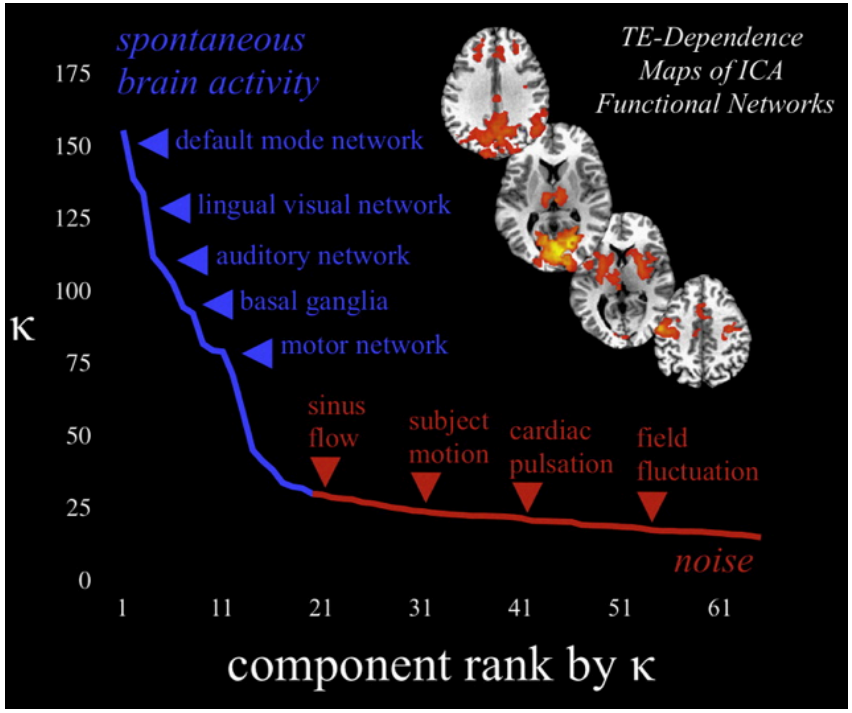
Eliminate noisy components

McKeown et al, 1998
Thomas et al, 2002

Spatial ICA

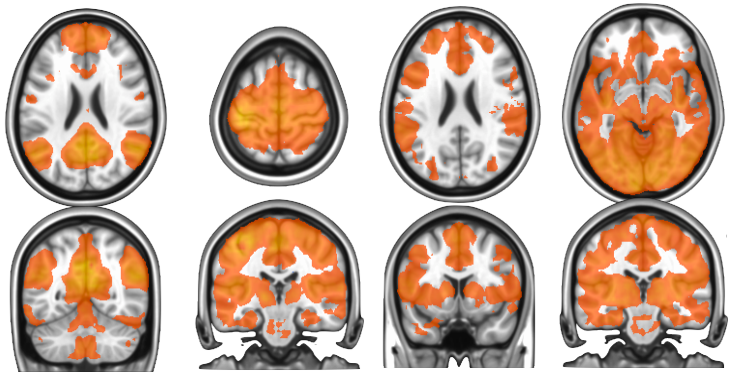
- How to objectively identify noise components?
  - Automatic classification based on spatial, temporal, frequency features (Tohka et al, 2008, De Martino et al, 2007)
  - Multi-echo EPI + ICA to identify non-BOLD components (Kundu et al, 2012)



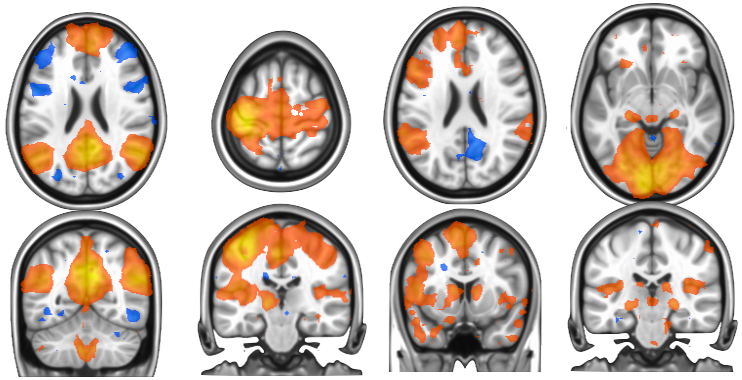


Multi-echo ICA denoising

Conventional / 1-sample T-test



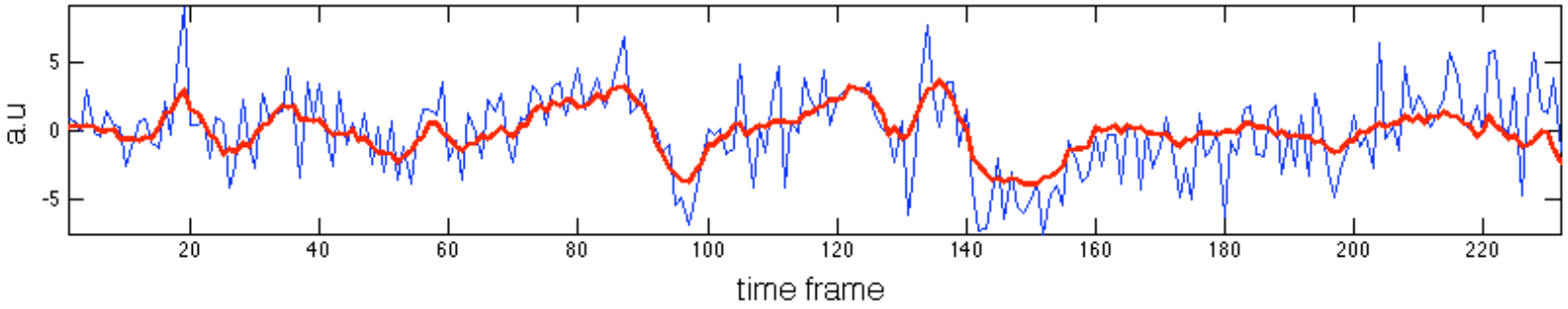
ME-ICA Coefficient Correlation / 1-sample T-test



courtesy Prantik Kundu

Band-pass filtering

"we band-pass filtered our data from 0.008 < f < 0.1 Hz"



- f > *xx* Hz (high pass):
  - motion drifts, scanner instability (but see also: J.W. Evans et al. OHBM 2013)
- f < *yy* Hz (low pass):
  - may help filter out physiological noise?
    - only "cyclic noise"
    - only if TR is short enough (no aliasing)
  - Signal of interest is low (hemodynamics)
    - Open question: 'interesting' resting-state activity at higher frequencies??

Resting-state fMRI at 4 Hz

Wednesday, June 19, 2013: 1:30 PM - 3:30 PM

Poster Number:

3480

On Display:

Wednesday, June 19 & Thursday, June 20

Authors:

Ying-Hua Chu[1], Shang-Yueh Tsai[2], Jyrki Ahveninen[3], Tommi Raij[3], Wen-Jui Kuo[4], Fa-Hsuan Lin[1]

Contrary to the prevailing view based on conventional resting-state fMRI studies limited to very low sampling rates, our results showed significant inter-hemispheric correlations even at frequencies above 0.1 Hz. Considering the power spectral density of a canonical hemodynamic response function, our results suggest that at 4 Hz, either the noise and signal are decreased in parallel, or other physiological signal exists, such that the contrast-to-noise ratio (quantified by the Z-score of the correlation coefficients) at 4 Hz is still about 60% of that at 0.1 Hz. While the spatial resolution of InI is somewhat

frontiers in
HUMAN NEUROSCIENCE

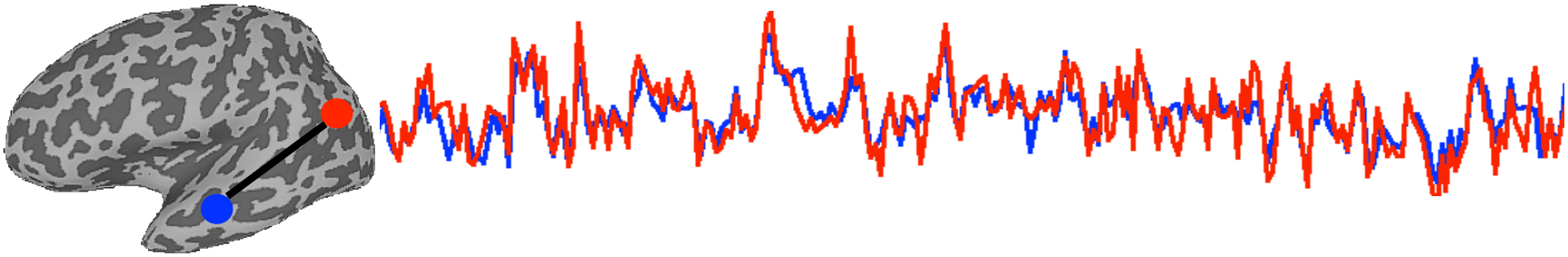
ORIGINAL RESEARCH ARTICLE
published: 01 May 2013
doi: 10.3389/fnhum.2013.00168

Beyond noise: using temporal ICA to extract meaningful information from high-frequency fMRI signal fluctuations during rest

Roland N. Boubela[1,2,3]*†, Klaudius Kalcher[1,2,3]†, Wolfgang Huf[1,2,3,4], Claudia Kronnerwetter[2,5], Peter Filzmoser[3] and Ewald Moser[1,2]

fluctuations alone. Consequently, the use of bandpass filters in resting-state data analysis should be reconsidered, since this step eliminates potentially relevant information. Instead, more specific methods for the elimination of physiological background signals, for example by regression of physiological noise components, might prove to be viable alternatives.

Summary



- Functional connectivity is based on relationships between fMRI time series of different regions
  - Assumption: shared temporal structure

    → neural interactions

- But, fMRI time series contains a mixture of neurally driven BOLD signal and **noise** (hardware, head motion, physiological processes ...)

- Must separate “signal” from “noise”

Summary, cont.

- Two classes of physio noise (cyclic,variations)
- Data-driven analyses can complement model-based methods
  - model & pattern discovery
  - when monitoring is not available
  - try to minimize bias (from data: non-gray-matter regressors; from researcher: objective criteria)
- Record physiological data
  - option to do physio corrections (now or later…)
  - understanding individual/group differences
- Physiological noise requires further study!

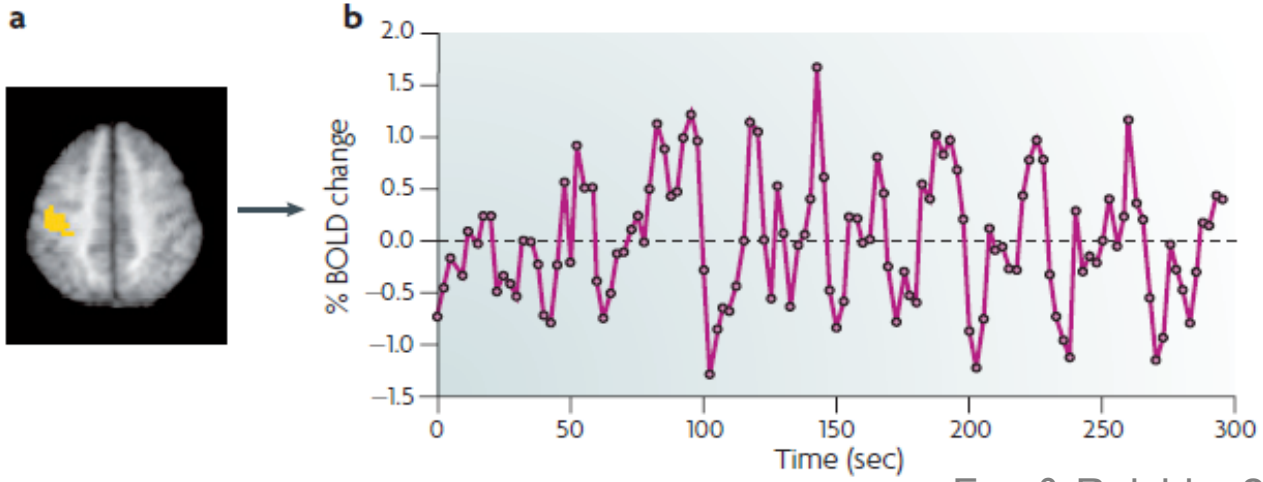
Reducing physiological noise

- Measurement-based approaches
  - RETROICOR (Glover et al, 2000)
  - RVTcor / RVHRCOR (Birn et al 2006,2008, Chang et al 2009)

- Data-driven approaches (physio + other noise)
  - CompCor (Behzadi et al, 2007)
  - PESTICA (Beall et al, 2007)
  - ICA (Thomas et al, 2002)
  - Multi-echo ICA (Kundu et al, 2012)

(and more...)

What is the signal?



Fox & Raichle, 2007

- noise in the fMRI signal (hardware, physiological, motion)
- fluctuations in intrinsic activity: *"ongoing neural and metabolic activity which is not directly associated with subjects' performance of a task*" (Raichle, 2009)

Understanding intrinsic fluctuations

- underlying neural processes?
  - relationship with electrophysiology
- influence on behavior?
  - interaction with tasks, subject responses
- relationship with anatomic connectivity?
  - DTI, lesion / patient studies, parcellation

Understanding intrinsic fluctuations

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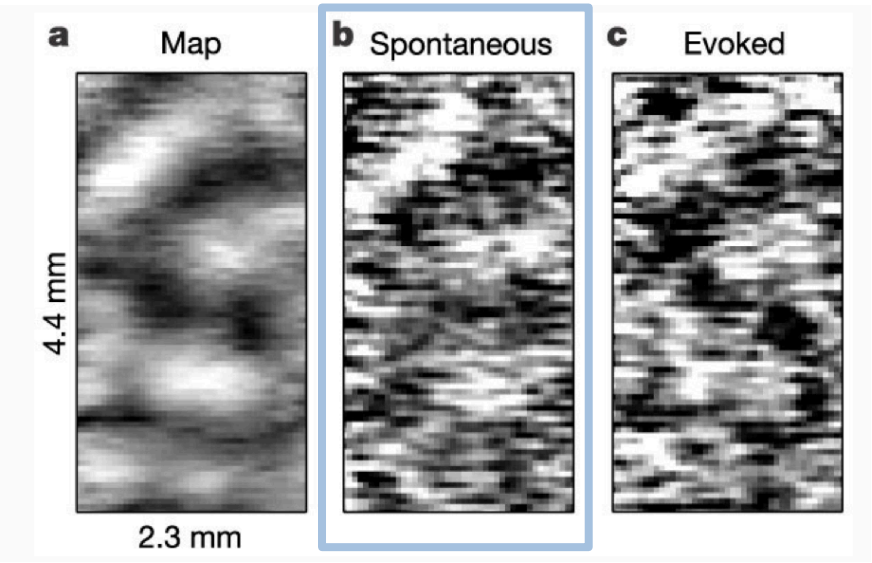
Electrical measurements of resting-state activity

- Electrical signals show intrinsic fluctuations and spatio-temporal organization

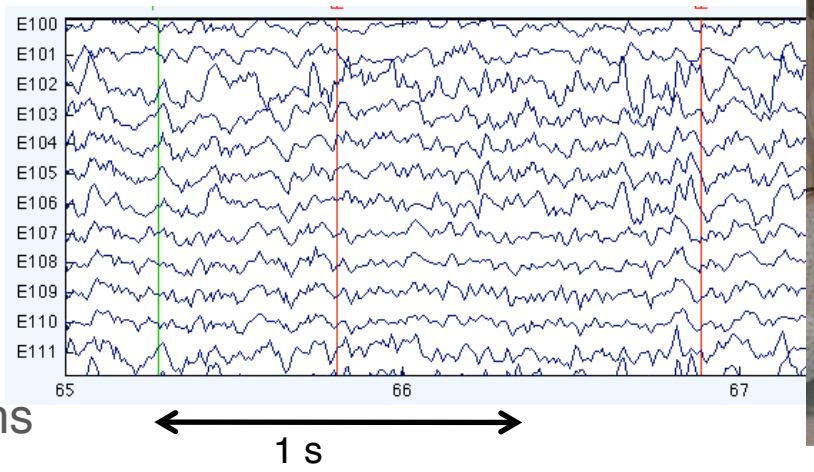


Kenet et al, 2003

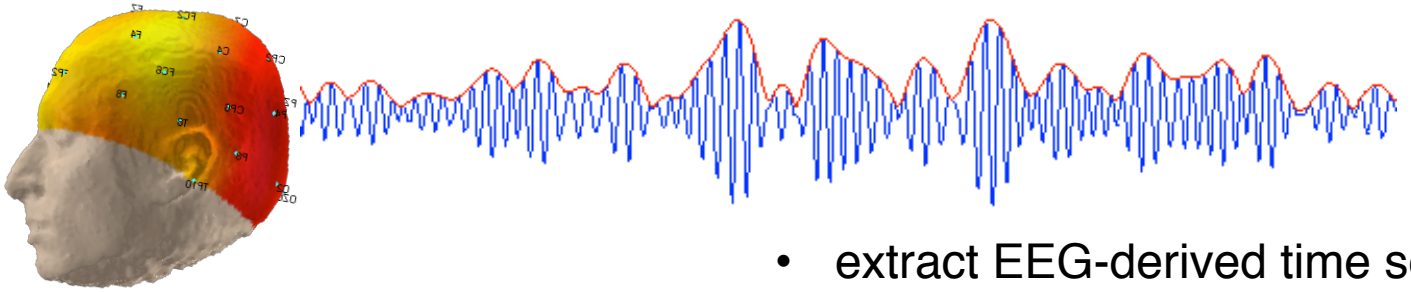
- Can try to relate resting-state BOLD & electrophysiological measurements (EEG, MEG, ECoG, depth electrodes...)
  - study events/states associated with BOLD fluctuations
  - higher temporal resolution
  - electrical (cf. hemodynamic)

Simultaneous EEG-fMRI

temporal res ~ ms
spatial res ~ cm



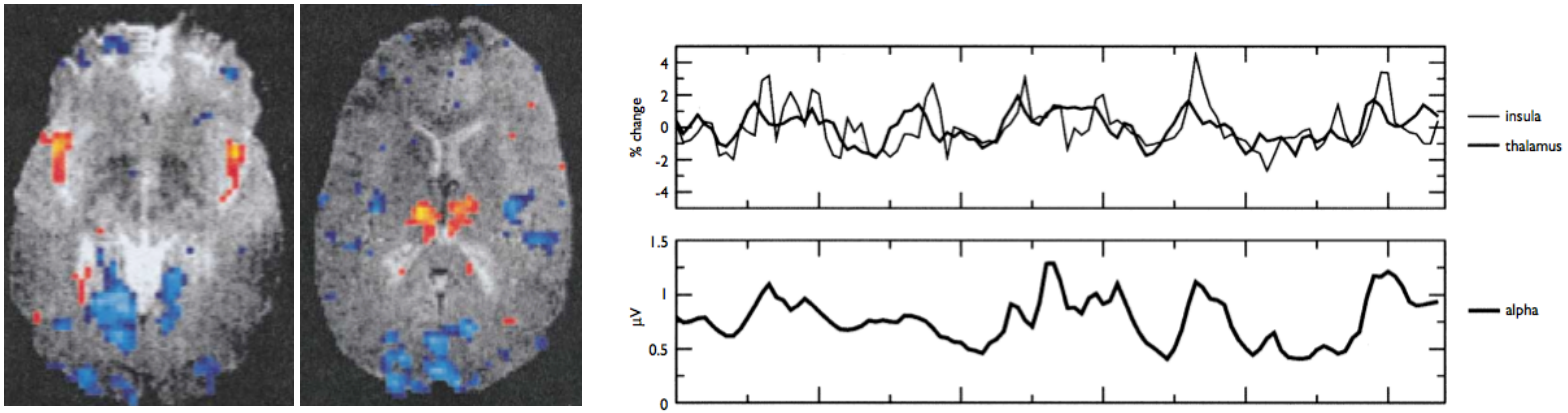
alpha rhythm (~ 10 Hz)



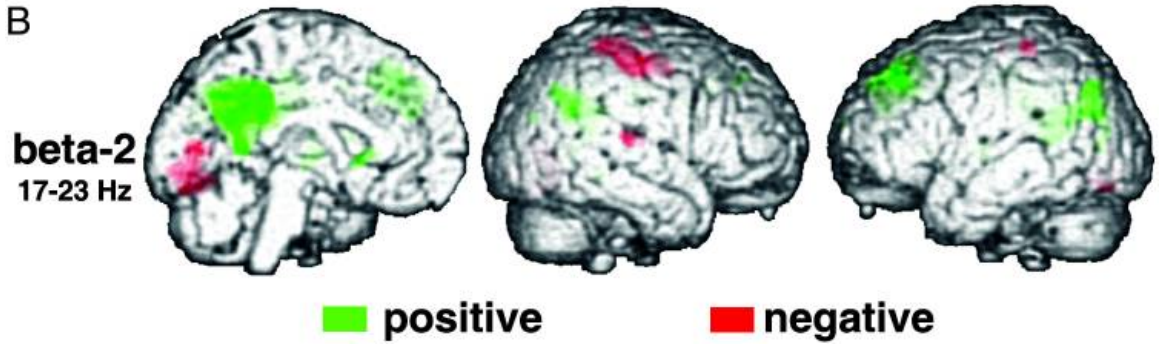
- extract EEG-derived time series(power, phase locking, etc.)
- convolve with HRF
- correlate with BOLD signal time series at each voxel

Resting-state EEG-fMRI correlations

correlations with alpha-band power fluctuations



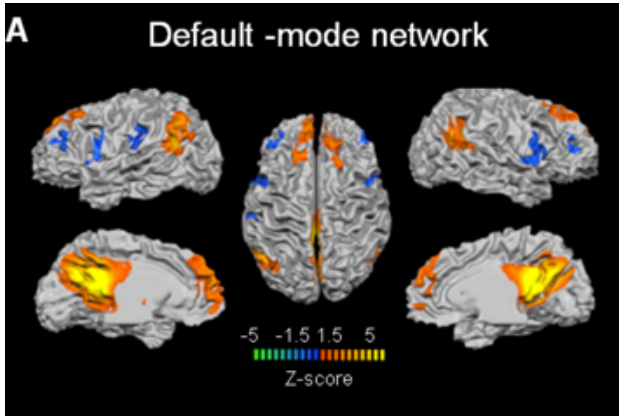
Goldman et al, 2002



correlations between beta power fluctuations &
fMRI Default Mode Network (Laufs et al, 2003)

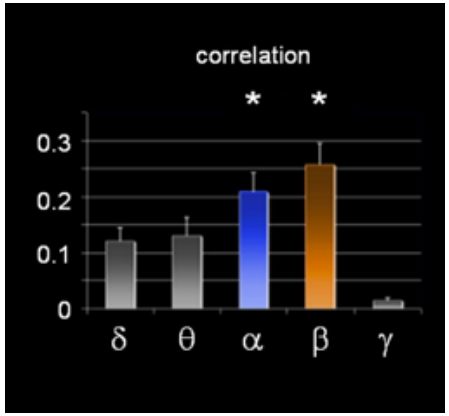
also see review article: Laufs, HBM 2008

Resting-state EEG-fMRI correlations?



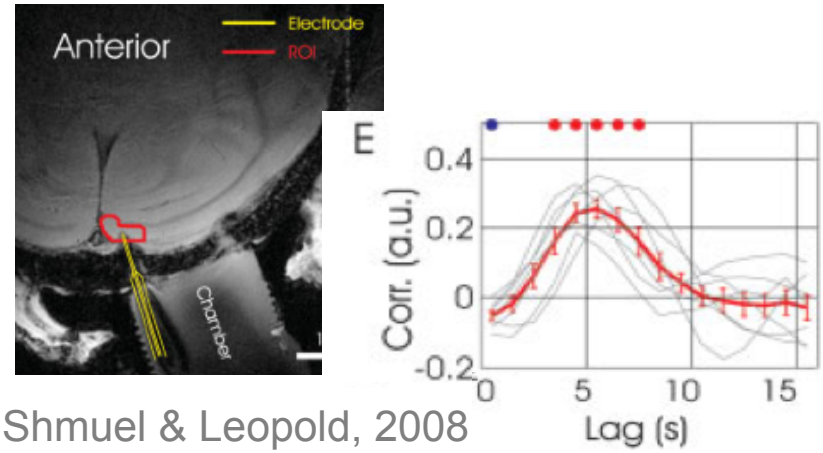
- Default-mode network reported to correlate (moderately) with:
  - upper beta (Laufs et al, 2003)
  - alpha & beta (Mantini et al, 2007)
  - frontal theta, inverse (Scheeringa et al, 2010)
  - decreased delta & increased beta (cross-subject) (Hlinka et al. 2010)
  - alpha (global phase locking)(Jann et al. 2009)

- Spectral "profile" rather than unique signature?
- Techniques under development



Mantini et al. 2007

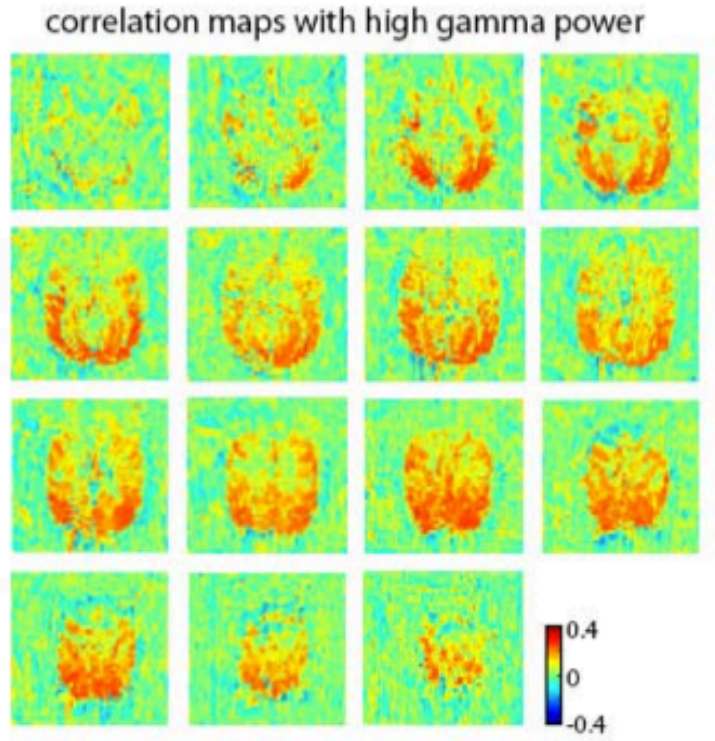
Simultaneous LFP-fMRI



Shmuel & Leopold, 2008

gamma power fluctuations in local field potential (LFP) found to correlate with fMRI signal

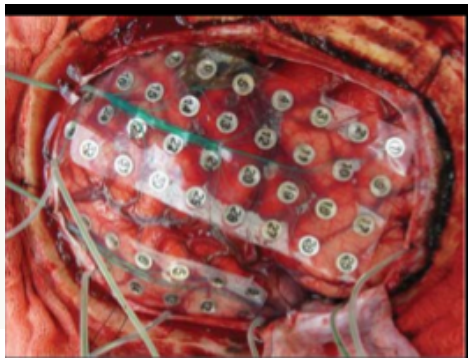
correlations are spatially widespread!



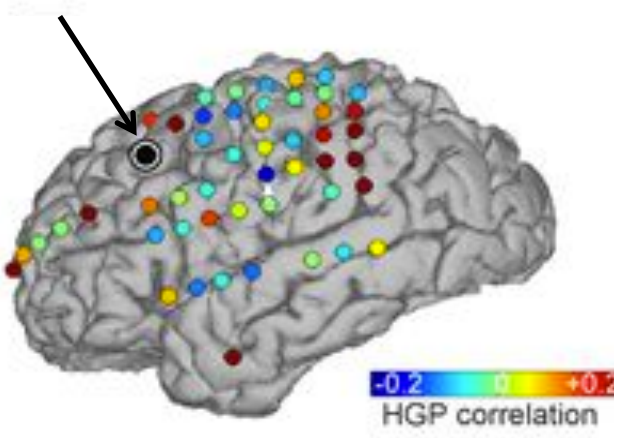
Scholvinck et al., 2010

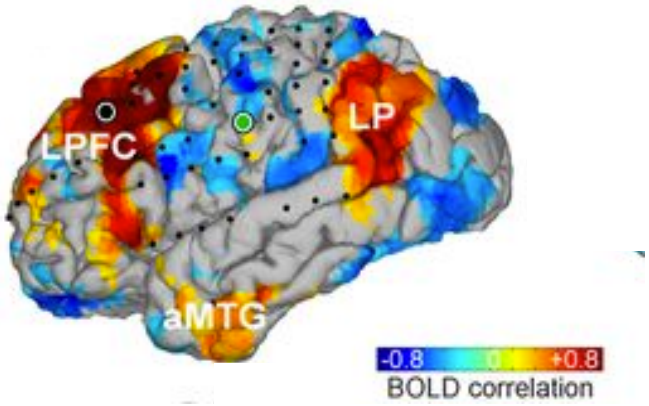
ECoG

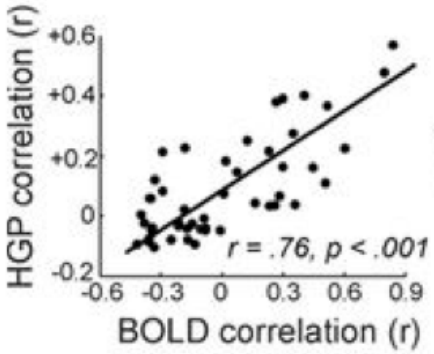
- invasive (implanted surface and/or depth electrodes)
- measure electrical activity with high spatial **and** temporal resolution



How well do “networks” of electrical signals match “networks” of BOLD fMRI?







Keller et al. 2013

- auditory network (Nir et al, 2008)
- sensorimotor network (He et al. 2008)
  - also with slow cortical potential (He et al, 2010)

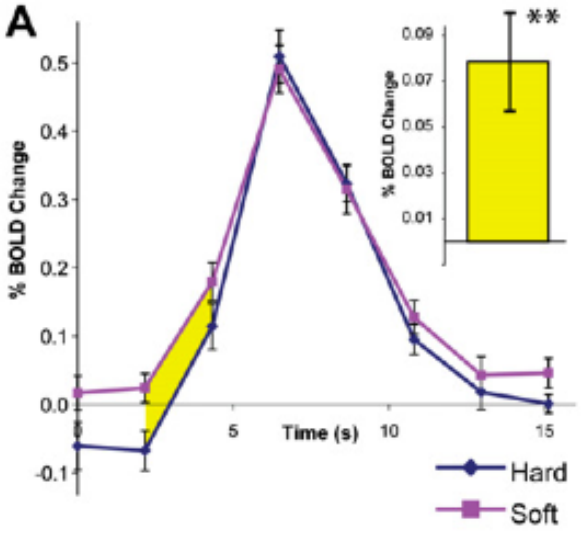
Understanding intrinsic fluctuations

- underlying neural processes?
  - relationship with electrophysiology
- influence on behavior?
  - interaction with tasks, subject responses
- relationship with anatomic connectivity?
  - DTI, lesion / patient studies, parcellation

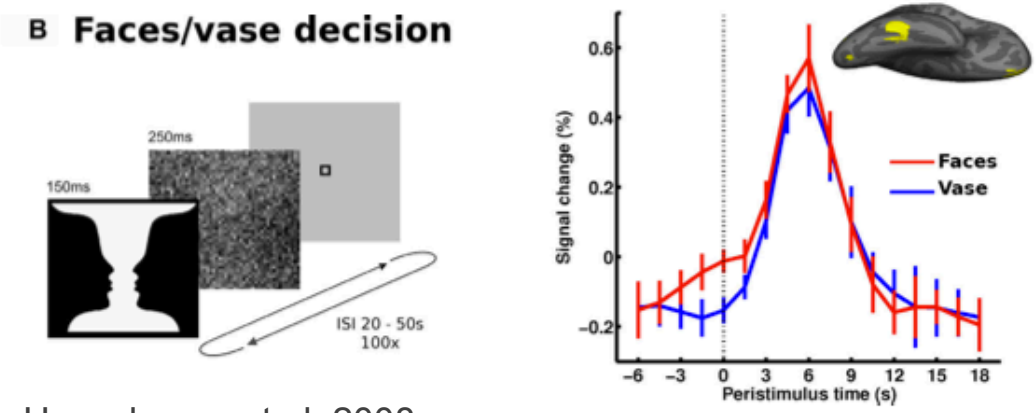
Influence of intrinsic activity on behavioral response

Reviewed in: Sadaghiani et al, 2010

Does pre-stimulus intrinsic activity predict subsequent response or perception?



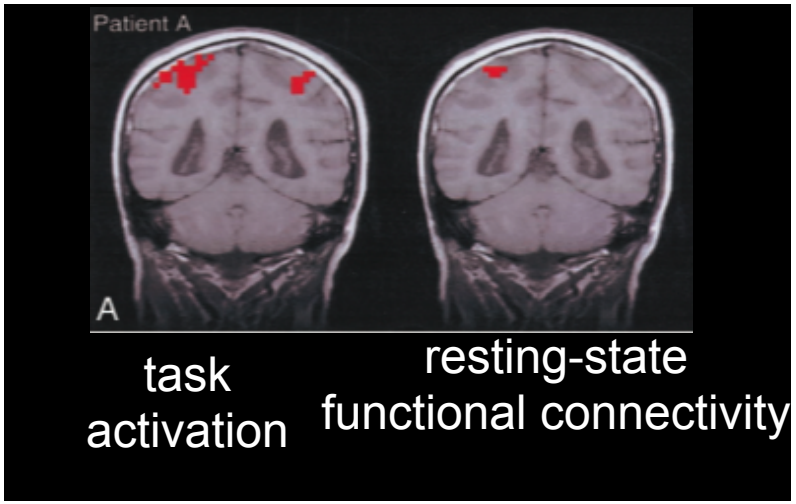
Fox et al., 2007

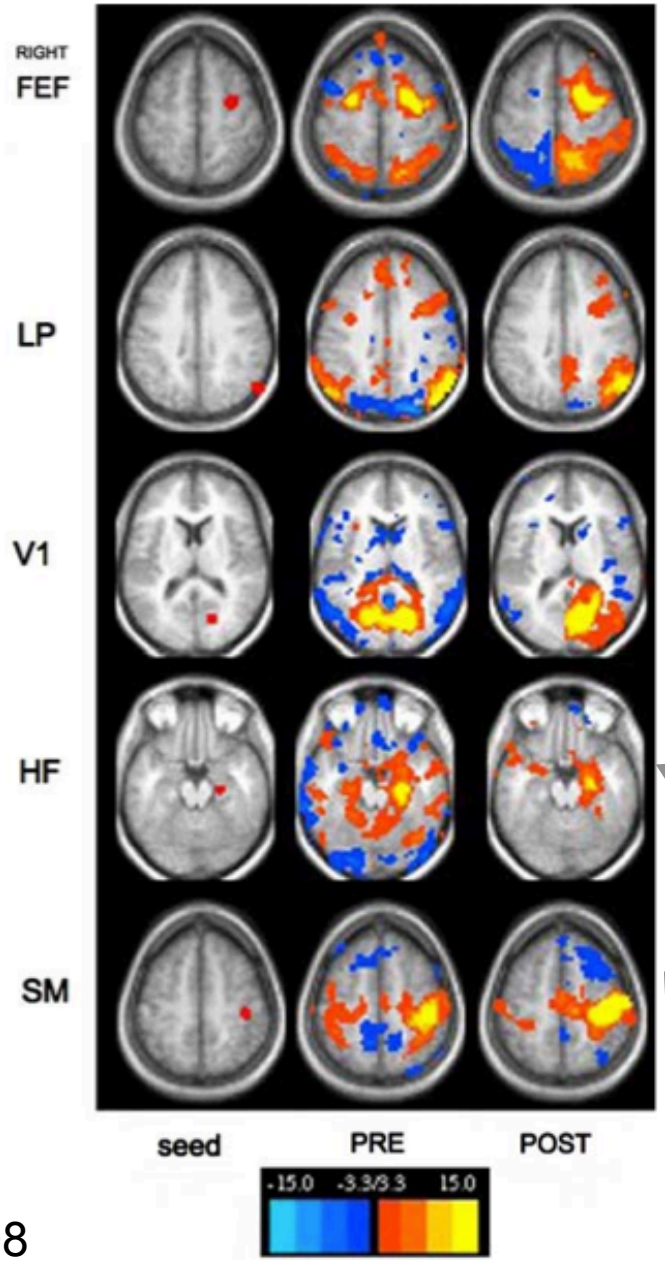


Hesselmann et al, 2008

Relationship with structural connectivity

Quigley et al., 2003



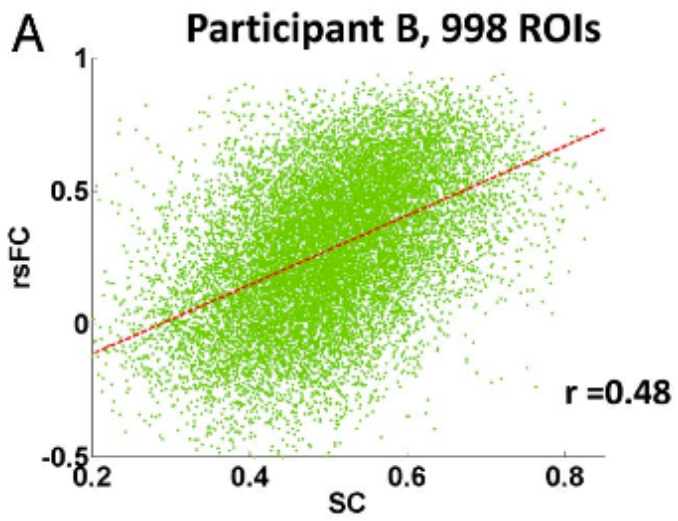


via indirect connections?

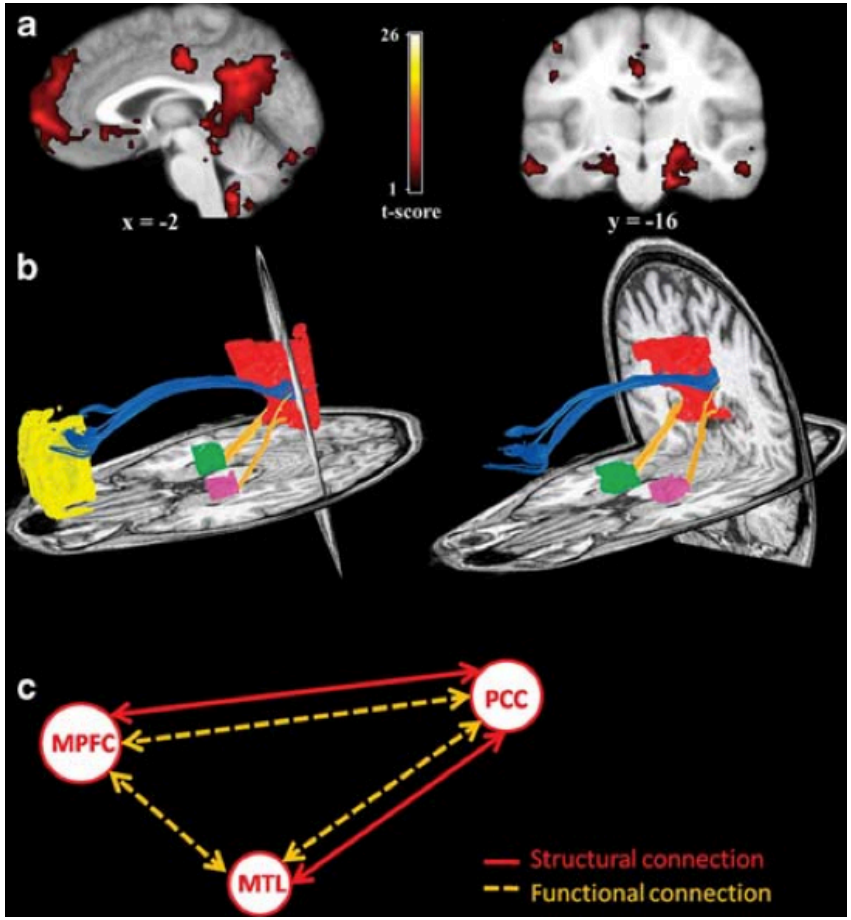
Johnston et al., 2008

Relationship with structural connectivity

Comparison with DTI: correlations between resting-state functional connectivity & white matter tracts

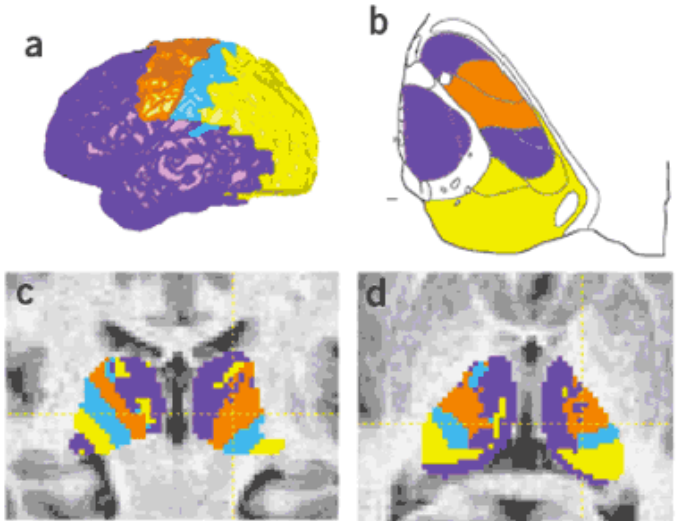


Honey et al. 2009

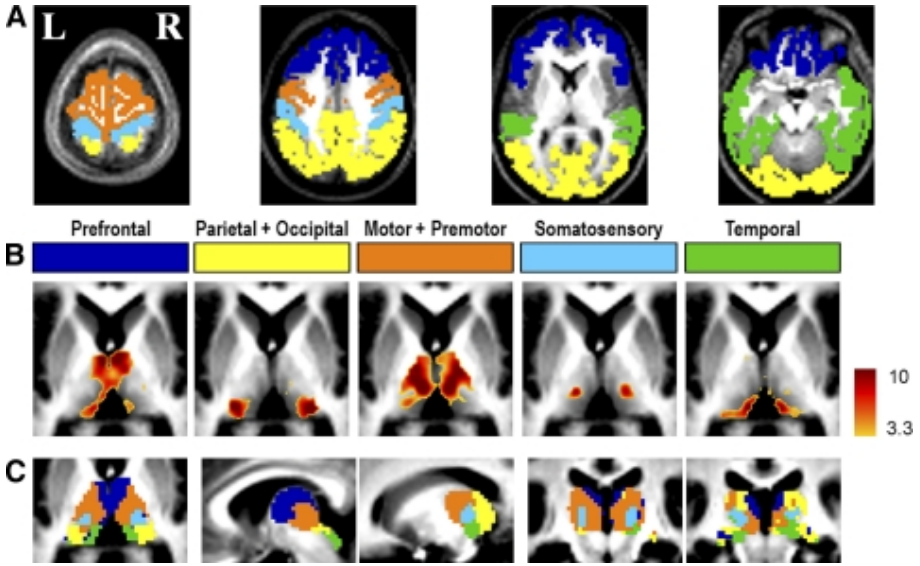


Greicius et al. 2009

Connectivity-based parcellation

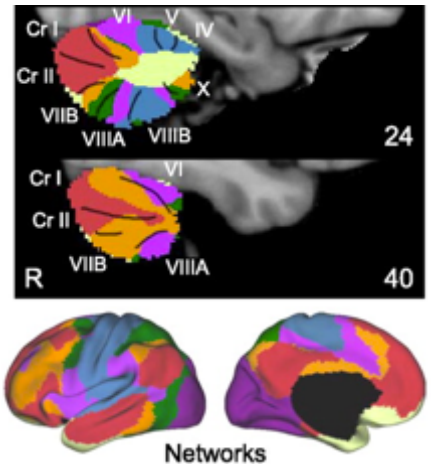


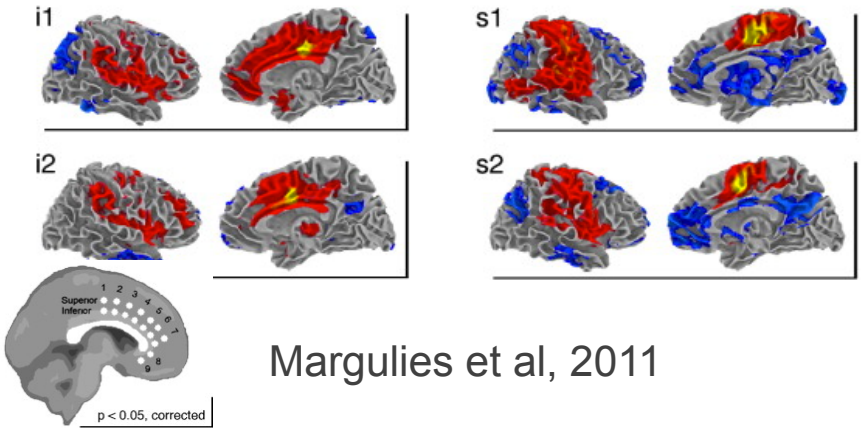
Behrens et al., 2003



Zhang et al., 2008

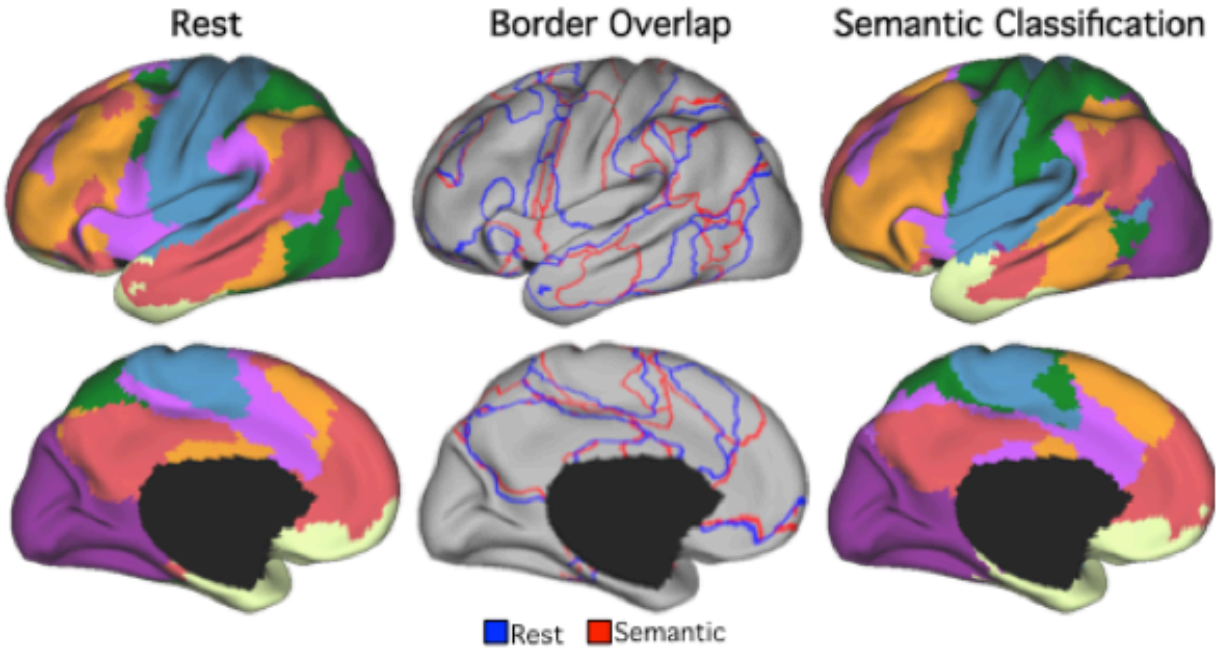
Buckner et al, 2011





Margulies et al, 2011

Variability of connectivity-based parcellation

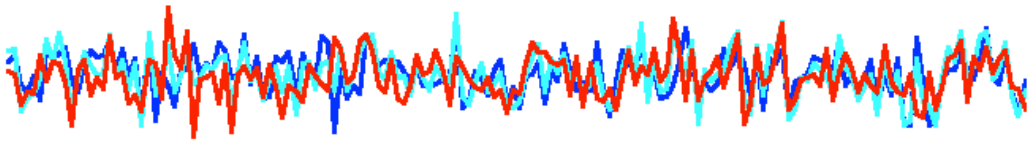


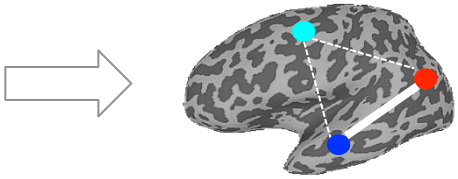
Krienan et al, OHBM 2013

Resting states

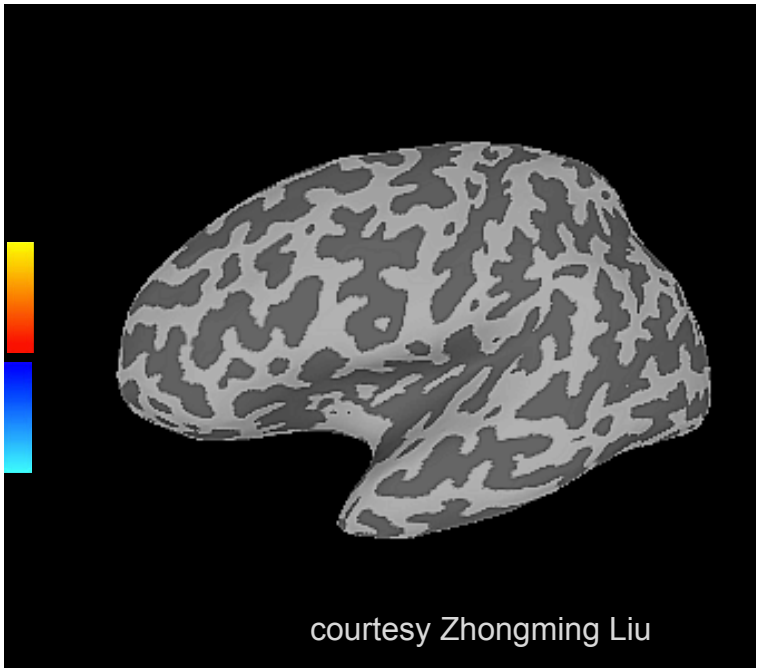
‘Static’ analysis

- One measure of FC per scan



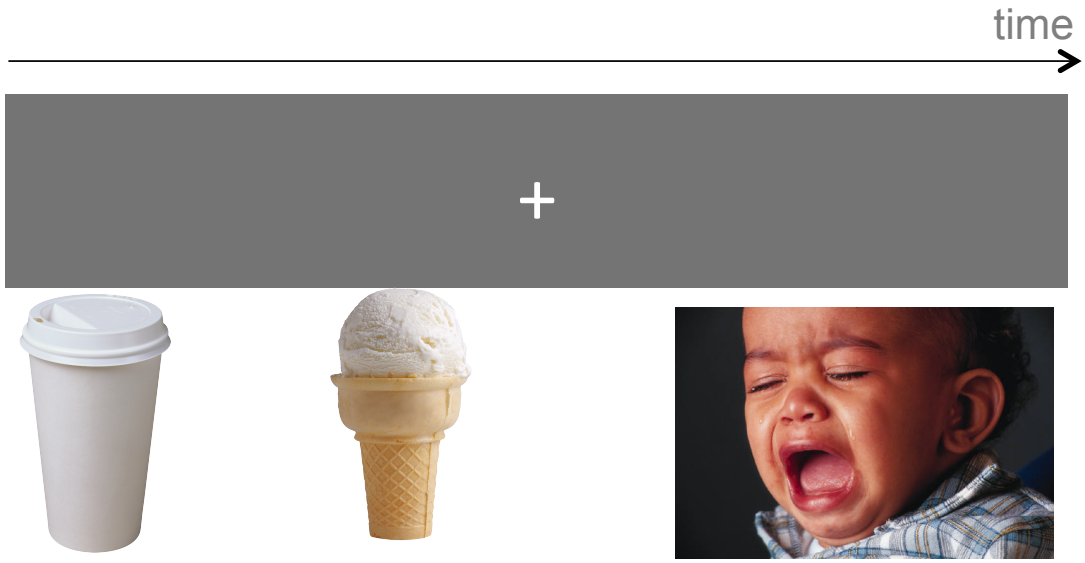


Resting-state BOLD activity

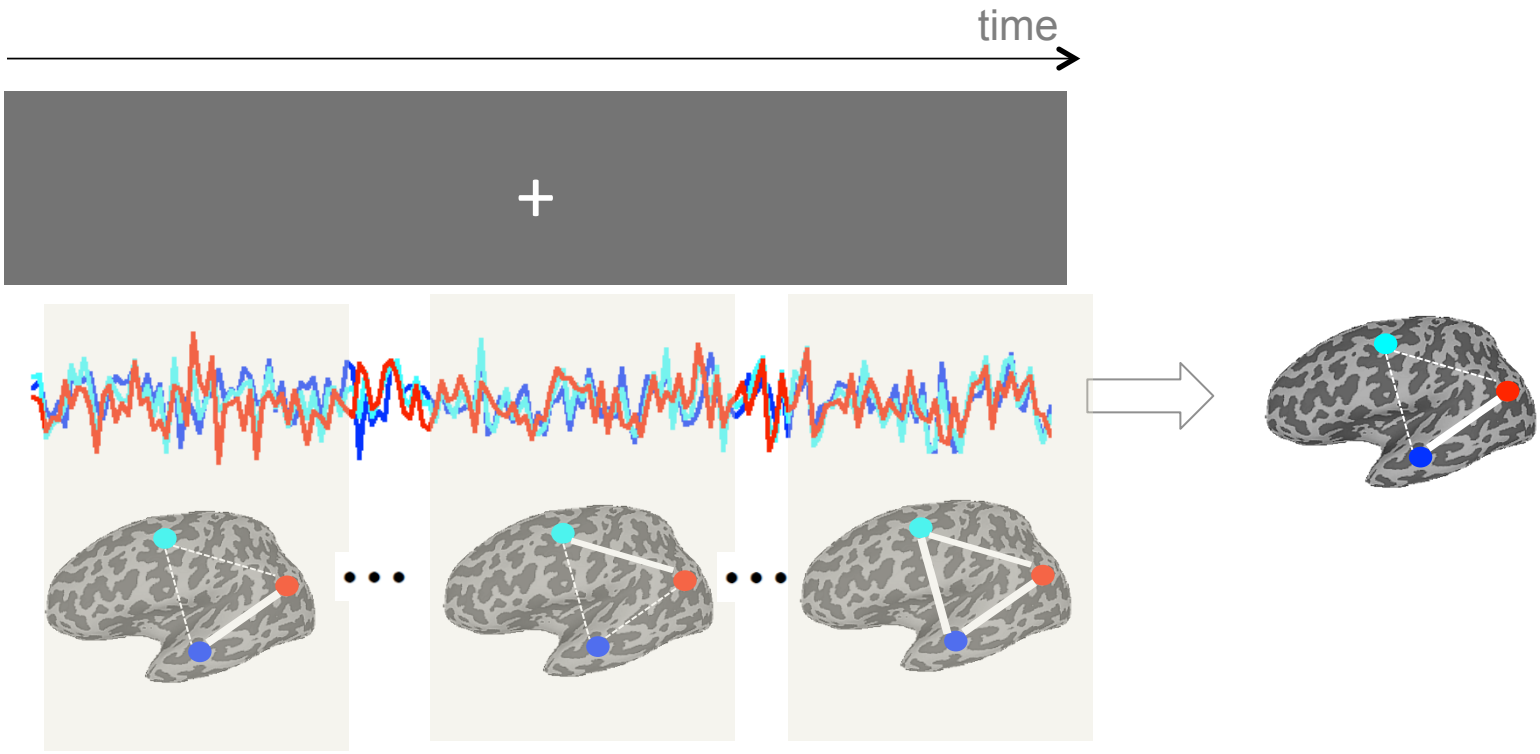


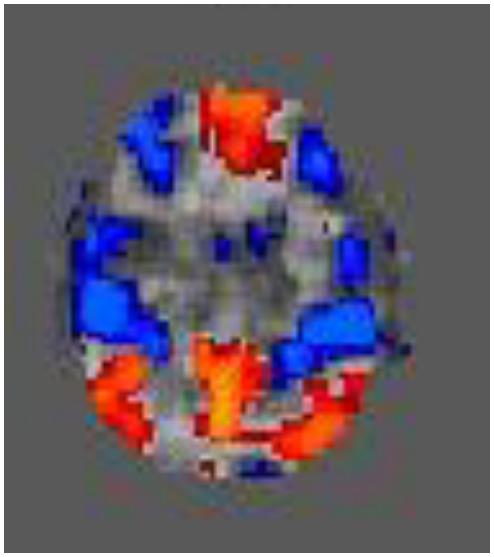
- Dynamic information?
- Within-scan variation in cognitive & vigilance states

- Static analysis: unexplained variance in FC due to changes in cognitive & vigilance states

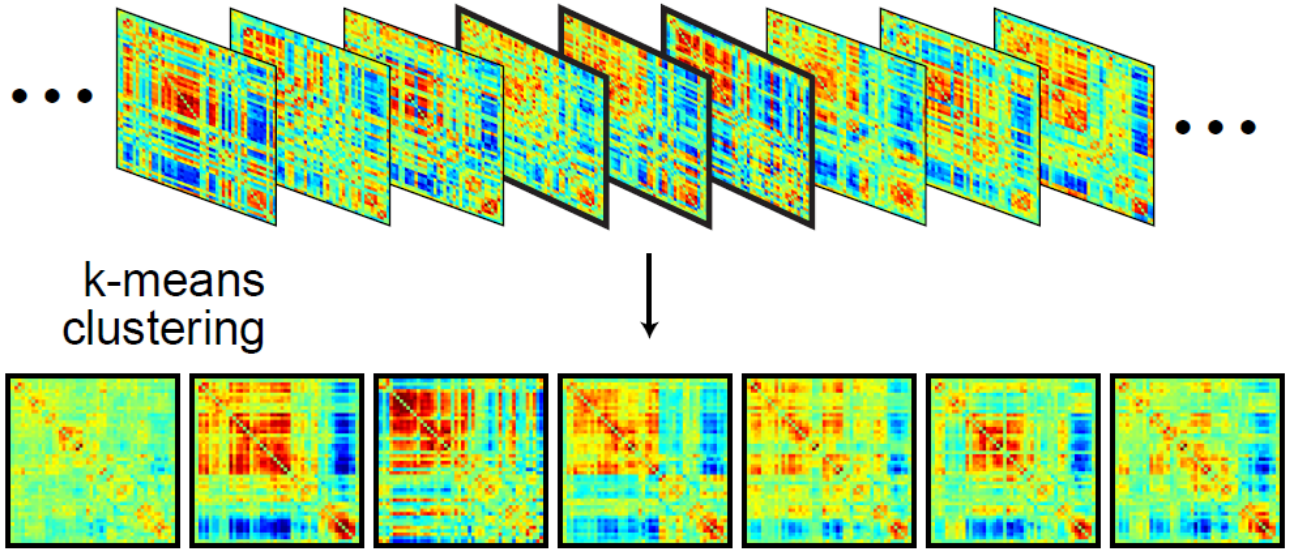


‘Dynamic’ analysis





Seed-based correlation, 2-min sliding windows

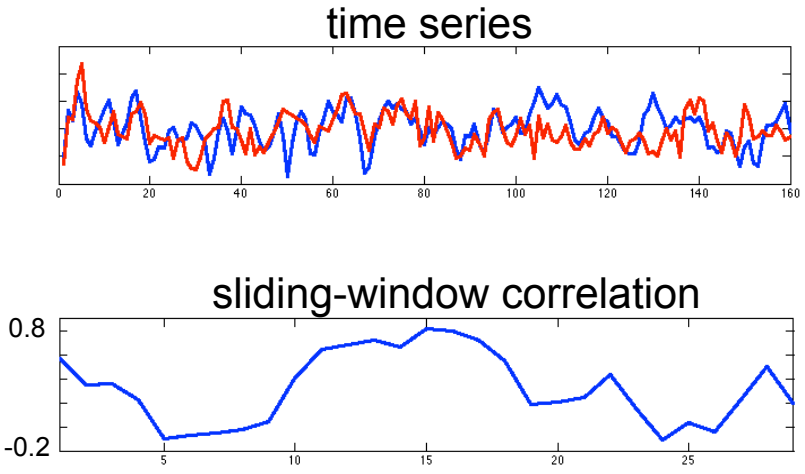


Allen et al. 2012

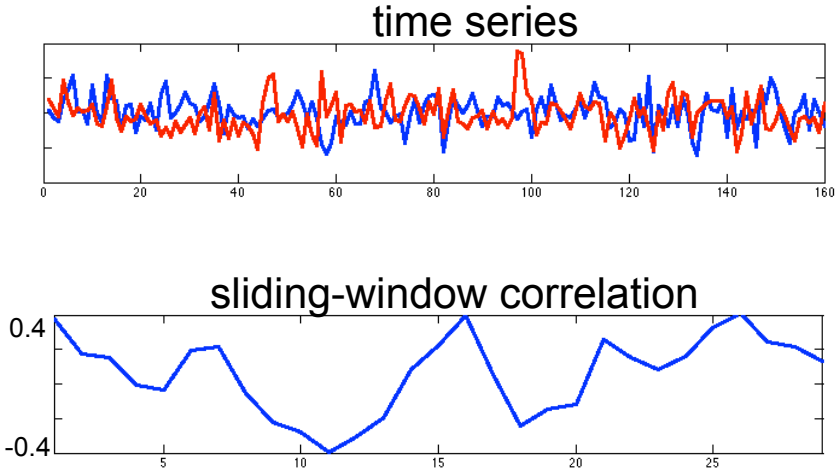
Spurious variability

- fMRI contains unknown mixture of neuronally driven BOLD signal and non-neuronal fluctuations
- Noise can cause spurious FC changes

fMRI time series (PCC, dACC)

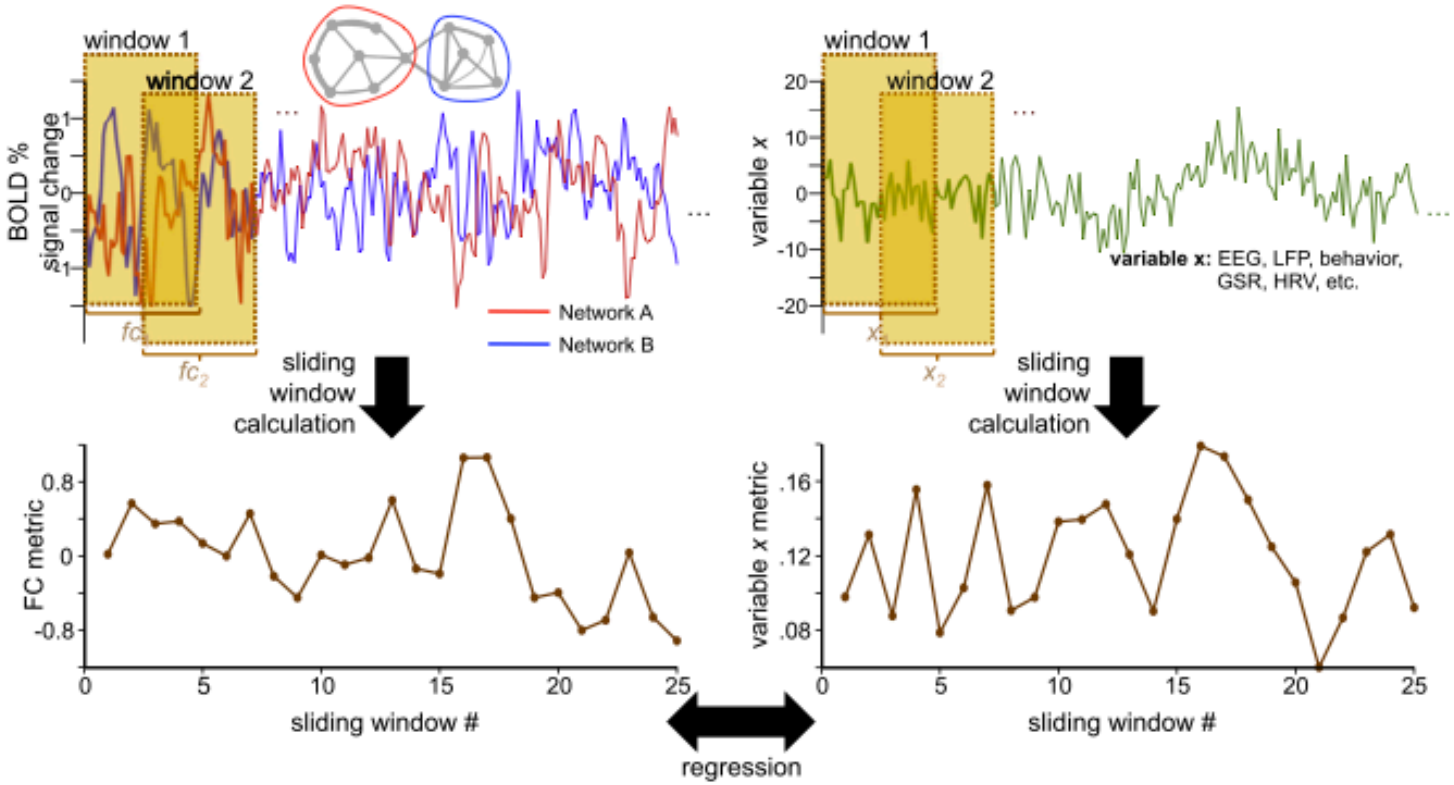


independent Gaussian white noise



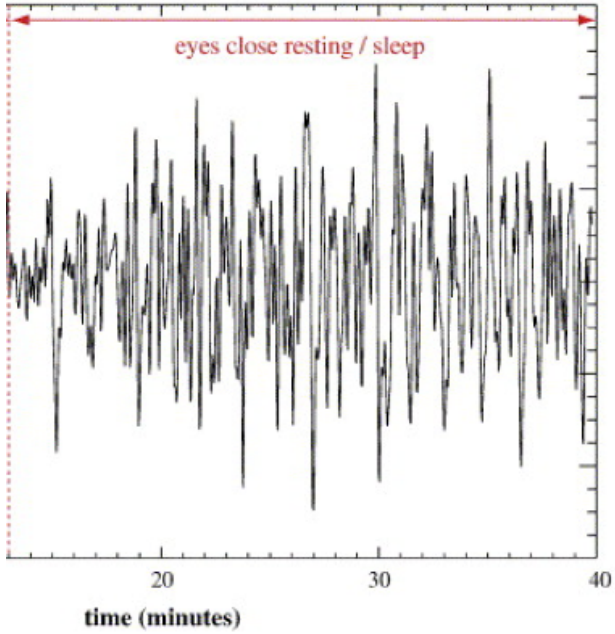
Correlates of time-varying BOLD FC

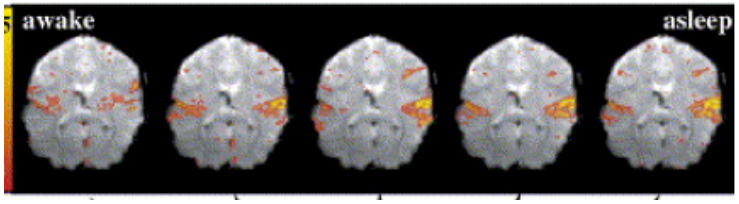
- Relate changes in FC to concurrent measurements (EEG, physiology, ...)



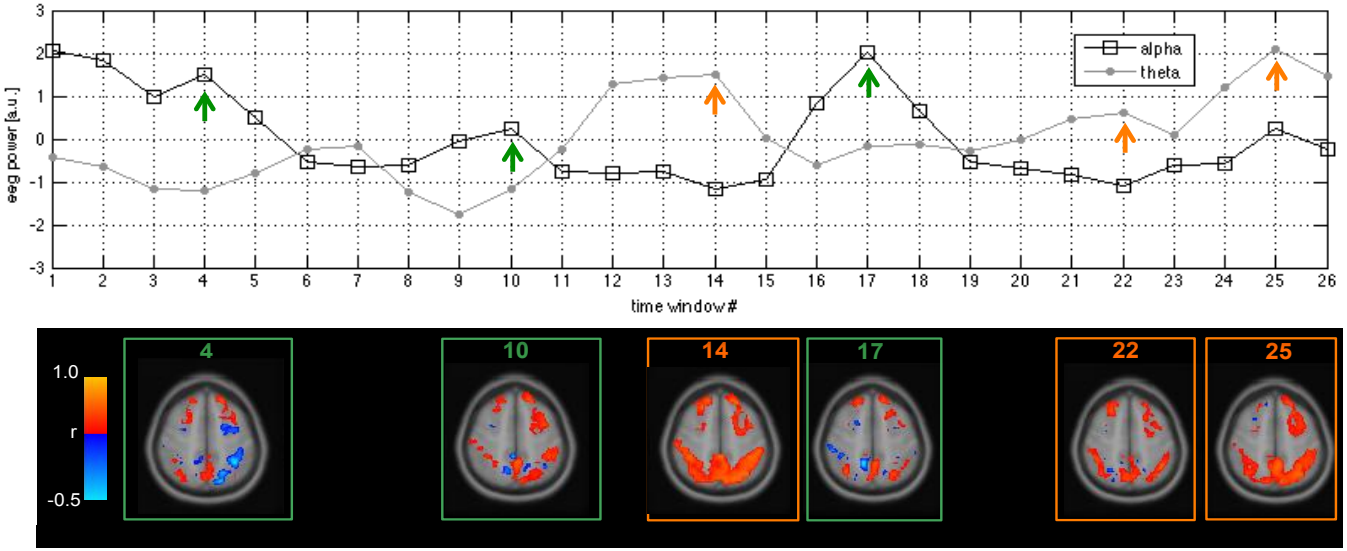
Hutchison et al. 2013
(review article)

Influence of vigilance state



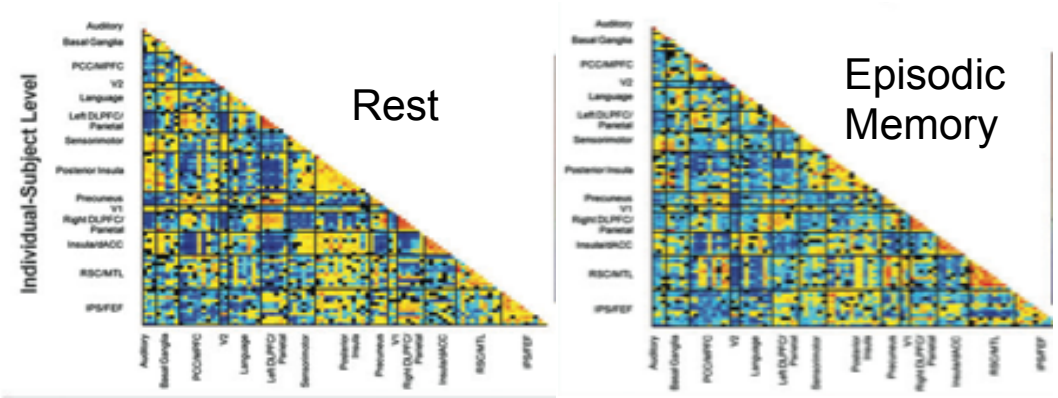


Fukunaga et al. 2006

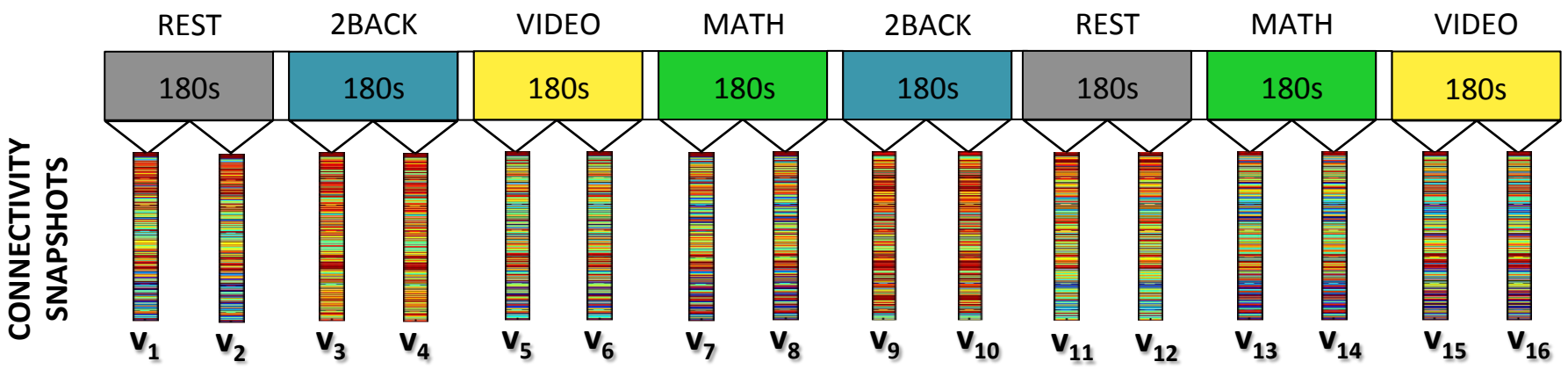


Chang et al. 2013

Influence of behavioral/cognitive state



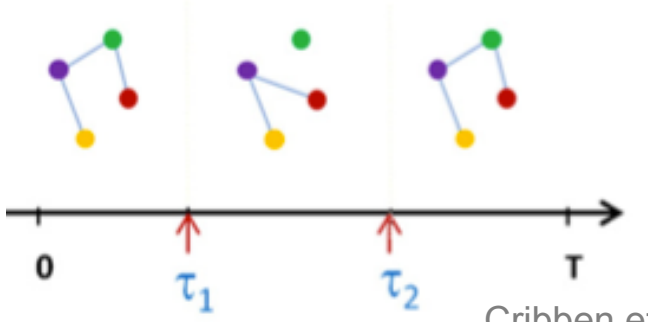
Shirer et al, 2012



Javier Gonzalez-Castillo

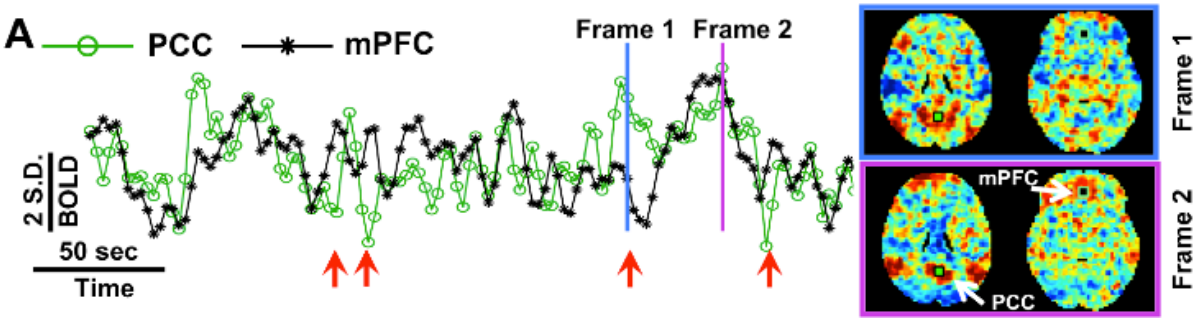
Dynamic analysis methods

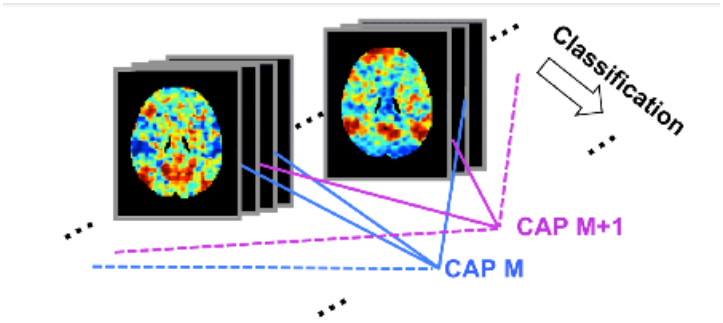
- "Dynamic connectivity regression" (Cribben et al.)

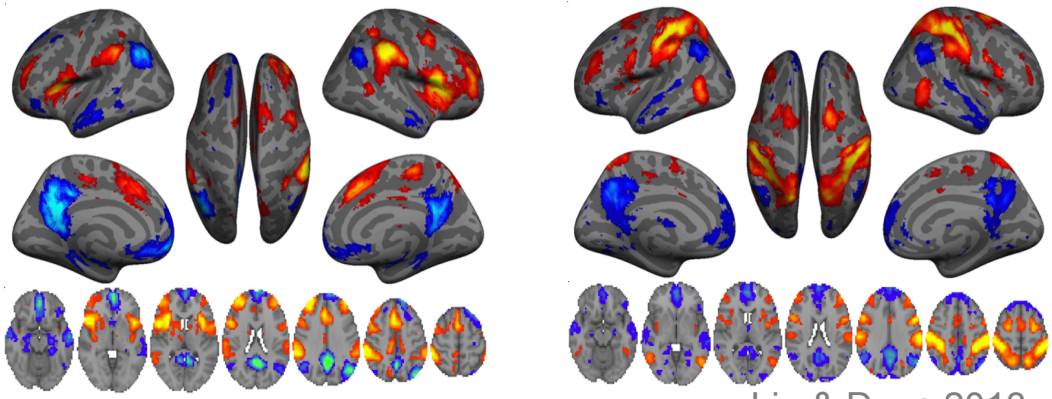


Cribben et al. 2012

- "Co-activation Patterns" (Xiao Liu)







Liu & Duyn 2013

- many others... active future direction

Thanks!

- Jeff Duyn & AMRI group
- Gary Glover
- Dan Handwerker
- Jennifer Evans
- Zhongming Liu